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CUTANEOUS MANIFESTATIONS OF SOME TROPICAL DISEASES

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NEW YORK

THE RECENT war has again brought to the attention of American dermatologists the need for a more intimate knowledge of tropical diseases. To obtain information on the incidence of certain of these diseases in the United States Armed Forces, I recently communicated with the Surgeons General of the Army and Navy. I had expected a reasonably large number of cases of cutaneous leishmaniasis (oriental sore) and even of leprosy but was surprised to learn that as many as 32 cases of yaws had been reported in Army personnel and 24 cases in the Navy and Marine Corps, a total of 56 cases contracted during World War II. Information was not given as to where the infections had been acquired or as to the race of the patients.

Of the five diseases which I shall describe briefly, three, namely, yaws (treponematosis), pinta and Carrion's disease, are almost entirely confined to the tropics, whereas cutaneous leishmaniasis and leprosy are more prevalent in tropical than in temperate climates.

YAWS (FRAMBESIA TROPICA)

Yaws is an infectious disease caused by Treponema pertenue, an organism discovered by Castellani in 1905, soon after the discovery of the causative organism of syphilis. Yaws is acquired usually by personal contact, especially in childhood, but at times certain flies may transmit it directly. Infection is not acquired venereally. Yaws is confined largely to the Negro and yellow races. It would appear that the comparative rarity of yaws in the white race is due to superior personal hygiene and not to racial immunity.

The initial lesion of yaws (the mother yaw) frequently appears on the lower part of the leg; however, it is not always present. The lesion does not remotely resemble the chancre of syphilis but is of the same type as the common secondary (frambesiform, or raspberry-like) eruption. It is usually the largest lesion present and is the size of a horse chestnut or even of a small apple.

The Distinguished Lecture in Dermatology, read before the Section on Dermatology and Syphilology at the Ninety-Seventh Annual Session of the American Medical Association, Chicago, June 24, 1948.

The common secondary eruption appears as a rule from six weeks to three months after infection. This eruption does not resemble a syphilitic lesion but looks like that of impetigo, many of the crusts being amber colored. A comparatively rare secondary eruption, of a lichenoid type, suggests to my mind the appearance of lichen scrofulosus.

A characteristic eruption is a hyperkeratosis of the soles and occasionally of the palms, spoken of in the West Indies as "crab yaws" because the patient is said to walk like a crab. This is a late secondary manifestation, often painful when secondarily infected. In a study of 1,614 syphilitic Negroes in Baltimore, Turner found no plantar hyperkeratosis, whereas such lesions were present in 48 per cent of 791 patients with yaws in Jamaica.

The most interesting feature of yaws for the dermatologist is its resemblance, in some respects, to syphilis. The causative organisms are morphologically identical; the serologic reactions are the same; both diseases yield to treatment with arsphenamine and allied drugs, bismuth and penicillin, and the tertiary destructive lesions of the two diseases are indistinguishable.

In spite of these striking similarities, there are many features which the great majority of authorities think sufficient to prove that syphilis and yaws are different diseases. Some of these are as follows: The infection in yaws is nearly always, if not always, extragenital, as apparently no patches appear on the mucous membrane of the genital organs. Intrauterine infection does not occur in yaws, children never showing lesions comparable to those of congenital syphilis. The initial lesions in the two diseases are strikingly different. The frambesiform eruption in yaws rarely has a counterpart in syphilis. Neither iritis nor alopecia of the "moth-eaten" type has been recorded in yaws. The disease is milder than syphilis because it does not attack to any great extent the vital structures of the body, such as the viscera and the cardiovascular and central nervous systems. The lesser tendency of yaws to attack the blood vessels may be seen in histologic sections of cutaneous lesions. There are differences between the immune reactions in the two diseases, though eventually there is complete cross immunity between them. Before the cross immunity is established, it is possible for human beings, and susceptible animals, to have the diseases simultaneously.

The treatment of yaws is in general like that of syphilis. In the mass treatment of native populations, bismuth preparations have been used instead of arsphenamine to save expense. As might be expected, penicillin has proved of great value in the treatment of yaws. Dwinelle

and his associates[1] reported recently on 500 cases of primary and secondary yaws observed for twelve months in Haiti. They considered penicillin, especially penicillin calcium in peanut oil and white wax U. S. P., the drug of choice on account of the short course of treatment and the results obtained.

PINTA

The term "pinta" is derived from the Spanish *pintar,* to paint, and, like many other tropical diseases, it has numerous local names. Pinta is mostly confined to tropical and subtropical areas of the Americas; it is most prevalent in Colombia and Mexico. In 1929 to 1931, a thorough survey was made by Gonzales Uruena in the southern half of Mexico, where pinta was present in a total of 270,685 persons (about 11 per cent of a population of 2,500,000). As this survey was made ten years before the causative organism was known, cases of the primary and secondary stages of the disease were of course not included; they would have considerably increased the total number.

The theory of fungous origin remained persistently in textbooks for forty years but had to be discarded when the causative treponeme was discovered. The theory was based on the work of Montoya y Flores, who made cultures from patients with carate (pinta) in Bogotá. Most of the fungi cultivated were of the genera Aspergillus and Penicillium, generally supposed to be nonpathogenic. In my work in Colombia and Mexico, I obtained these same fungi.

The first discovery which suggested a spirochetal rather than a fungous origin was that of Menk, who in 1927 obtained positive Wassermann reactions in nearly 75 per cent of the patients with pinta at the United Fruit Company's hospital in Santa Marta, Colombia. Register obtained positive reactions in 80 per cent of 207 patients with pinta in the same hospital; and, in 1930, a Mexican commission under the leadership of Gonzales Herrejón obtained positive reactions in 97 per cent of patients. Other reasons for discarding the theory of fungous origin were: With one possible exception, pinta had not been successfully produced in human beings or animals from cultures obtained from patients with the disease; when patients with pinta left the endemic areas the same organisms could not be cultured, though the lesions remained, and in rare cases the lesions of pinta are located on one side of the body ("hemipinto"), which factor would practically exclude a cutaneous fungous infection. I agreed with the members of the Mexican commission in excluding a fungous causation and suggesting one possibly

1. Dwinelle, J. H.; Sheldon, A. J.; Rein, C. R., and Sternberg, T. H.: Evaluation of Penicillin in the Treatment of Yaws: Final Report, Am. J. Trop. Med. **27**:633-641 (Sept.) 1947.

due to spirochetes. Finally, it was noted that the disease was amenable to antisyphilitic treatment. All these indications of spirochetal rather than fungous causation were known at least eight years before the spirochetes were discovered and the matter of causation settled.

The second, and most important, discovery was that of the causative treponeme by Grau Triana and Armenteros on Aug. 3, 1938 in Habana, Cuba . Two days later, the same organism was observed in a patient by Pardo-Castello, and soon the discovery was universally recognized.

The other important discoveries were made by León y Blanco, a pathologist of Habana who spent three and a half years in Mexico, beginning in October 1938. He demonstrated the presence of the treponemes in 2,000 patients with pinta, as well as the absence of the organisms in healthy persons in the same region. Of special importance was the experimental transmission of pinta from man to man, first carried out by León y Blanco on himself and later on 27 volunteers. Twenty-three other experiments in transmission were performed in Mexico, Cuba and Brazil. León y Blanco not only first proved the inoculability of pinta from one human being to another, but was the first to note an initial lesion, often followed with lesions of dissemination, which he called "pintids" (a secondary stage).

In a summary of his most recent report, León y Blanco stated the belief that the initial lesion of pinta is a papule which appears from three to sixty-one days after intracutaneous inoculation, the average time being fourteen to twenty days.[2] Experimental reinfection in treated patients was successful on four occasions. One patient had an outbreak of pintids on the one hundred and forty-second day after inoculation. Of nine inoculations in cases of latent seropositive syphilis, four were successful; León y Blanco seemed to think this result indicated partial cross immunity. Superinfection could not be obtained experimentally in patients with late manifestations of pinta (dyschromic stage).

The initial lesion may be the sole cutaneous change for a period of three months to a year. It may resemble the lesions of psoriasis, tinea corporis or lichenified eczema. It never ulcerates and is often surrounded by smaller satellites, which may finally coalesce and become incorporated with the larger lesions. The neighboring lymph nodes are slightly enlarged and hard and on puncture show numerous treponemes.

The lesions of the secondary stage ("pintids") first appear as smooth, lenticular macules or miliary papules, pink or violescent and

2. León y Blanco, F.: Experimental Pinta, read in a Symposium, National Institute of Health, United States Public Health Service, Washington, D. C., April 8-9, 1948.

slightly scaly. The number of lesions varies from a dozen to about a hundred. The secondary lesions tend to coalesce and form patches resembling the lesion of psoriasis, tinea corporis, eczema or the annular lesions of syphilis. They may last for months or years. León y Blanco had observed his own secondary lesions for nearly three years, when they disappeared under treatment.

Serologic reactions are always negative during the primary stage, but become positive a few days after the appearance of secondary lesions in 60 per cent of cases. In cases of the late (dyschromic) stage the serologic reactions are positive in close to 100 per cent.

Previous to the discovery of the causative treponeme, the primary and secondary lesions could not have been scientifically recognized, the belief being that the dyschromic (late) stage constituted the entire course of the disease. The late stage is better called dyschromic than pigmentary, as the terminal stage is one of complete depigmentation. Many descriptions of the colors of the lesions of pinta are misleading. Actually, there are only two striking colors: a leaden or slate blue, and white. The blue lesions occur as freckles or diffuse areas, the usual sites being the exposed parts of the body, especially the bony prominences of the face and extremities (fig. 1). The amount of scaling in these late lesions is difficult to evaluate, as is the degree of pruritus. Itching is not a prominent feature of the disease. The course of the dyschromic stage is extremely chronic unless treatment is given (fig. 2). In 1 patient whom I saw in Mexico the disease had been actively present for forty-two years.

The treatment of pinta is similar to that of the other treponemal diseases, syphilis and yaws. As the disease is apparently transmitted from one person to another by close contact and as there is no known insect carrier or other vector, prophylaxis depends on personal hygiene.

The prognosis of pinta is good as to life, with the possible exception of cases, such as some recorded in Cuba, in which changes in the spinal fluid and the aorta may conceivably affect the duration of life. The eruption yields well to antisyphilitic treatment until the stage of complete depigmentation (vitiligoid stage) is reached, when treatment is of no avail.

LEISHMANIASIS

Leishmaniasis has for a number of years been divided into two types: (1) that seen in the Old World, and known as cutaneous leishmaniasis, oriental sore, Aleppo boil or Biskra button, and (2) that which occurs in the Western Hemisphere, known as American (mucocutaneous) leishmaniasis.

Cutaneous Leishmaniasis.—According to Russian investigators, whose work has recently come to light,[3] there are apparently two independent types of cutaneous leishmaniasis (oriental sore), in addition to the mucocutaneous (American) type. Of the two Russian types, one is moist, is found in rural areas and has a short incubation period, with acute ulcers occurring five to ten days after infection and a duration of less than six months. Parasites are scanty and a reservoir is present in wild rodents (chiefly gerbils). The dry type is a disease of

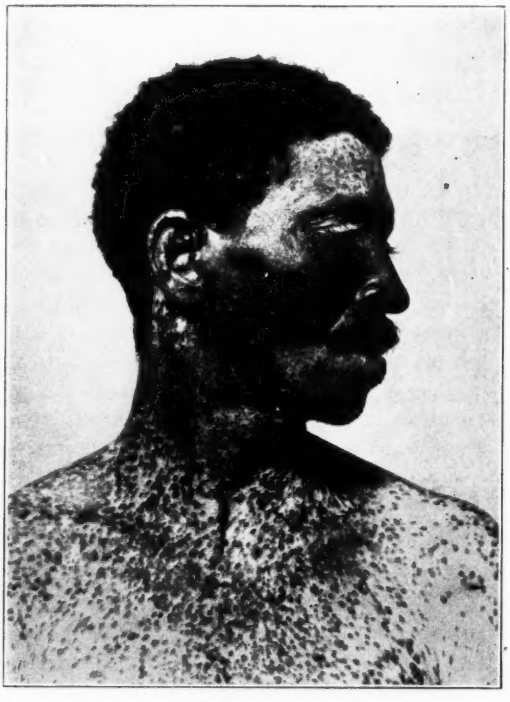

Fig. 1.—Pinta. Extensive eruption of the face and trunk in a man aged 36, of mixed Indian and Negro descent. The face showed diffuse bluish black pigmentation; the trunk was mottled with areas of depigmentation and areas of bluish pigmentation on the normal skin. This case was observed in Santa Marta, Colombia (Fox, H., in Bercovitz, Z. T.: Clinical Tropical Medicine, New York, Paul B. Hoeber, Inc., 1944).

towns; it is found throughout the year, has a longer incubation period and is more chronic. Parasites are numerous and human beings are probably the reservoir.

3. Hoare, C. A.: Cutaneous Leishmaniasis (Critical Review of Recent Russian Work), Trop. Dis. Bull. **41**:331-343 (May) 1944.

The eruptions mentioned in the preceding paragraph are caused by protozoa called leishmaniae, in honor of Colonel Sir William Leishman, who first discovered the causative organism of kala-azar. All these protozoa are morphologically indistinguishable in microscopic examination of scrapings and on culture.

The geographic habitat of oriental sore is widespread, including parts of Africa, Asia and Europe. In Africa the disease is mainly seen

Fig. 2.—Pinta. Extensive eruption of twenty-five years' duration in a woman 30 years old. Few blue areas remain on the face; complete depigmentation has taken place on half the body.

on the coast of the Mediterranean. In Asia Minor it is especially common in Palestine, Syria and Armenia. The disease is also endemic in the southern and eastern parts of Asia and Europe, and in Greece, Italy, Sicily, Cyprus and Crete. This incomplete list includes numerous locations where members of the Armed Forces were exposed to the disease during World War II.

The report I received from the Army indicated that 422 men had been infected with oriental sore. Major Haverty, Chief of the Technical Information Office, wrote that the data contained were preliminary and subject to change on completion of tabulation of medical records. Ball and Ryan [4] published an account of 499 proved cases of oriental sore in the American military personnel in the Middle East; the locale was probably Persia. The report from the Navy and Marine Corps included a total of 16 cases of leishmaniasis, of which 4 were of kala-azar, 3 of oriental sore, 1 of American leishmaniasis and 8 of an unspecified form.

Oriental sore may occur in persons of any age, of either sex and apparently of any race. The disease may be contracted either through the bite of some species of sandfly (Phlebotomus) or through personal contact, as from one child to another. Other insects, including the housefly, may occasionally transmit the disease mechanically. Berberian proved that the stable fly can act in the same manner. Dogs often have the disease and may act as a reservoir for the parasites. The gerbil was recently proved to act in the same way in parts of the Union of Soviet Socialist Republics.

The incubation period may vary greatly, from a few weeks to many months or, at times, to more than a year. The eruption begins as small papules, which enlarge and form button-like plaques, varying from 2 or 3 to 6 or 8 cm. in diameter. Eventually, the lesions soften and exude a sticky material, which dries to form adherent crusts. When the crusts are removed, a pinkish, edematous border is seen. In some cases of the dry type no ulceration occurs. The eruption never suggests the appearance of a boil, the common term Aleppo boil being a misnomer. The number of lesions varies from one to occasionally one hundred or more. One patient had three hundred lesions, but the average number is only two or three.

Oriental sore is as a rule a self-limited disease, as the Turkish name *habel-seneh* ("button of one year") indicates. The lesions are chiefly seen on the exposed parts of the body, mainly the face and limbs (fig. 3). They occasionally affect the lips, but they rarely appear on the trunk and never on the palms, soles or hairy scalp. Healing is apt to produce permanent scars, often rather deforming.

In an infrequent case the lesions will persist for years and assume a tuberculoid structure histologically, as opposed to the ordinary picture of a nonspecific granuloma. In other rare cases relapses may occur; until lately these have resisted all treatment.

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4. Ball, D., and Ryan, R. C.: Cutaneous Leishmaniasis, Bull. U. S. Army M. Dept. **79**:65-73 (Aug.) 1944; abstracted, Trop. Dis. Bull. **42**:19-20 (Jan.) 1945.

Oriental sore does not affect the general health and is practically devoid of constitutional and subjective symptoms. There are no complications except secondary infection and frequent scarring.

The diagnosis is difficult at times as the manifestations of the disease may resemble those of tuberculosis, syphilis, ecthyma or bromoderma, or tropical and other ulcers. An unequivocal diagnosis can be made only after finding the organisms in smear preparations stained with Wright's method or in cultures. When these methods fail, intracutane-

Fig. 3.—Oriental sore in a boy of 12 years, from Allepo, Syria, observed at Ellis Island (Fox, H.: Two Cases of Oriental Sore [Cutaneous Leishmaniasis], New York M. J. & M. Rec. **116**:365 [Oct. 4] 1922).

ous tests with material from killed parasites (leishmanin test, Montenegro's test) may be helpful, positive reactions having been obtained in nearly 100 per cent of cases. In 47 cases of recurrent leishmaniasis the parasites were demonstrated by Dostrovsky and Sagher in only 4, whereas the intradermal test gave a positive reaction in all but 1.

In regard to treatment, care should be taken to obtain the best cosmetic results, as the disease is not a serious one. Of the numerous chemotherapeutic remedies, quinacrine hydrochloride U. S. P.

(atabrine®) seems especially good. Marchionini [5] treated 300 patients in Ankara. In the early cases, in which parasites were present, the disease yielded to injections into or around the lesions of 1 to 2 cc. of 10 to 20 per cent solutions of quinacrine hydrochloride. Failure followed treatment in many chronic cases in which no leishmaniae were present. Good results were also obtained with quinacrine hydrochloride by Russian investigators and others. Bobrov claimed good results in treatment of the moist type of cutaneous leishmaniasis with application of wet dressings of blood: The ulcers healed, after five or six dressings, in two to three weeks.

Physical methods of treatment include roentgen irradiation, application of solid carbon dioxide and, recently, the use of grenz rays (roentgen rays of 2 angstrom units). Application of solid carbon dioxide has been highly recommended, as it gives quick results and requires no elaborate apparatus. Using grenz rays, Dostrovsky and Sagher claimed excellent results in treating the relapsing (tuberculoid) type, which had hitherto resisted all methods of treatment. There were no further relapses in 42 cases.

Mucocutaneous Leishmaniasis.—The American (mucocutaneous) type of leishmaniasis is well named, as it is present in every country of South America except Chile and in several countries of Central America, especially Guatemala, and the Yucatán peninsula of Mexico. The disease occurs most often in Brazil, especially in the states of São Paulo and Bahia, and next in frequency in Peru, Paraguay and Bolivia.

Like many tropical or semitropical diseases, it has a wealth of names, such as Bauru ulcer and Bahia ulcer (Brazil), espundia and uta (Peru), forest yaws (British Guiana), Bosch yaws (Dutch Guiana), pian bois (French Guiana) and "ear ulcer of the *chicleros*" (Yucatán and Guatemala). A total of twenty-three names have been recorded in South America, including six in Peru. One of the six Peruvian names (espundia) has unfortunately been used frequently though it is almost unknown in Brazil, where the causative organism was first discovered and where the disease is most frequent.

The most suitable name for the causative organism, which was discovered in 1909, is Leishmania braziliensis. This organism is morphologically identical with those that cause other forms of leishmaniasis. There are, however, certain laboratory differences and unquestionable clinical differences produced by this organism.

In all probability the disease is usually contracted through the bite of some species of Phlebotomus though it may at times spread from man

5. Marchionini, A.: Treatment of Oriental Sore, Schweiz. med. Wchnschr. **71**:1220-1223 (Oct. 18) 1941; abstracted, Trop. Dis. Bull. **40**:125 (Feb.) 1943.

to man by contact. There is no known reservoir for the vector, in contrast to oriental sore, for which the dog is at times a reservoir. Dogs, cats, monkeys and guinea pigs have, however, been experimentally inoculated with American leishmaniasis.

Like other types, American leishmaniasis may occur at any age and in any race, or in either sex. It is largely an occupational disease, occurring principally in men, especially among foresters, workers on tea plantations in Paraguay and those who collect chicle for chewing gum in the forests of Yucatán and Guatemala. The disease is usually contracted in moist tropical regions with virgin forests and luxuriant vegetation. However, the uta type, which shows no involvement of the mucous membranes, is seen on both slopes of the Andes at altitudes of 3,000 to 8,000 feet. According to Escomel, it also differs from the American type in that permanent immunity does not remain after healing.

The clinical forms of the disease may be divided into those which affect the skin alone and those which affect only the nose and throat. According to Klotz and Lindenberg, involvement of the nose and throat occurs from eight months to fifteen years after the appearance of the cutaneous lesions. In the opinion of these authorities, involvement of the mucosa is due to metastasis through the blood stream rather than to transfer of organisms with the fingers. This opinion is based on the long interval between the involvement of the skin and that of the mucosa, which often takes place after the ulcers have healed. Evidence against this view is the absence of visceral lesions and the fact that leishmaniae have not been demonstrated in the blood.

In a minority of cases the cutaneous lesions do not ulcerate, but occasionally become verrucous and suggest the appearance of tuberculosis verrucosa cutis. The involvement of the mucous membranes is serious on account of its chronicity and destructive tendency. Da Silveira noted lesions in the nose, throat and mouth in 20 per cent of 15,000 patients observed in the state of São Paulo, Brazil.

In making a clinical diagnosis one must consider blastomycosis, syphilis, tuberculosis, sporotrichosis and tropical ulcer. A point of differentiation from blastomycosis, when laboratory methods fail, is that blastomycosis does not yield to antimony potassium tartrate U. S. P. (tartar emetic). To differentiate the nasopharyngeal type, one must consider lupus vulgaris, yaws, rhinoscleroma, nasal myiasis and leprosy.

Treatment for the cutaneous lesions has been intravenous administration of antimony potassium tartrate, first introduced in 1911. Martins de Castro [6] stated in his correspondence with me that in Brazil stibophen

6. Martins de Castro, A.: Personal communication to the author.

N. F. (fuadin®) was considered the best remedy, eparseno® (an arsphenamine-like preparation containing dextrose and neutralized with piperazine) being added when the mucosae were involved. Eparseno, a French preparation, is said to be the same as preparation 592 in Ehrlich's series. However, it is expensive and was not available during the war.

The prognosis of American leishmaniasis is invariably good for the cutaneous lesions and usually so when the mucosae are involved and receive proper treatment.

CARRION'S DISEASE

The term Carrion's disease includes two strikingly different types of the same disease, which has probably existed in Peru for centuries and has recently been observed in Colombia, Equador and Guatemala. The varieties are known as verruga peruana, which is characterized by papular and nodular lesions of unusual interest to dermatologists, and Oroya fever, which is a severe constitutional disease.

Little was known about verruga peruana until 1870, when a railroad was built over the Andes from Lima to Oroya. A terrifying epidemic occurred in which 7,000 nonimmune Chilean laborers died; 100 British and American engineers also contracted the disease, and half of them died. Opinions about this new epidemic varied, some persons thinking, correctly, that it was a severe type of verruga.

In 1885, a brilliant Peruvian medical student, Daniel A. Carrion, allowed himself to be inoculated, against the advice of his friends, with apparently harmless verruga peruana, and died of Oroya fever after thirty-nine days. The experiment of Carrion proved that the disease was inoculable in man and that verruga peruana and Oroya fever were probably different phases of the same disease.

In 1909, Alberto Barton, another Peruvian, announced the discovery of the causative organism in the red blood cells. The organism was named Bartonella bacilliformis by Strong in honor of Dr. Barton.

Successful cultures on semisolid mediums, first obtained by Noguchi and Battistini in 1926 at the Rockefeller Institute, made it possible to prove beyond doubt that verruga peruana and Oroya fever were different phases of the same disease. Noguchi inoculated monkeys with a culture from a patient with Oroya fever and obtained only lesions of verruga. On the other hand, Mayer and Kikuth inoculated monkeys with material from a patient with verruga and produced, not only verruga peruana in some of the animals, but also the picture of Oroya fever, with death in 2 of the animals. The converse of Carrion's experiment occurred in a physician in Lima who accidentally pricked his finger while giving a blood transfusion to a patient dying of Oroya fever: Fortunately, the harmless type (verruga) developed, and he

recovered. From these facts it seems clear that verruga peruana and Oroya fever are different phases of the same disease.

Carrion's disease occurs at all ages, in both sexes and in all races. The disease runs a mild course in children up to 10 years of age, but becomes severe in adolescents and adults. Most of the inhabitants of infected ravines have the disease in childhood and thereby acquire a permanent immunity.

After two years of investigation (1912-1914) in the Rimac valley of Peru, Townsend concluded from entomologic evidence that the disease was transmitted by a species of sandfly, which he named Phlebotomus verrucarum. Townsend's work was soon confirmed by Shannon, who added a second species, which he named Phlebotomus noguchi. This organism lives out of doors, while Phlebotomus verrucarum is a domestic species; both are night-flying insects. All nonimmune visitors to infected areas are likely to contract the disease if they spend one or more nights without taking precautions against the bites of sandflies.

Human beings with active lesions constitute one reservoir of infection. It is also possible that persons without outward signs of the disease may act in the same way. As it had been suggested that certain plants might act as reservoirs, Maldonado made a botanical survey in 1930 in ravines where the disease was endemic and observed that certain lactescent plants had the same habitat as the sandflies. Three years later, Mackehenie and Coronado, using aseptic precautions, obtained from the latex of these plants cultures of organisms apparently identical with the bartonellas.

The chief pathologic changes in the Oroya fever type are hemorrhage and thrombosis in most tissues of the body. Bartonellas have been cultured from most of them, especially those of the spleen, kidneys, lymph nodes and bone marrow. According to Strong and his co-workers, the histologic structure has a sarcomatous, myxomatous or angiomatous (cavernous) appearance.

The two clinical forms of Carrion's disease, Oroya fever and verruga peruana, warrant separate descriptions, which follow:

Oroya Fever.—The period of incubation in Oroya fever varies from fifteen to forty days. (In Carrion's case, it was twenty-one days.) After a prodromal period of malaise, there is a sharp rise of fever of the remittent type, the temperature being usually between 100 and 102 F. and rarely rising above 104 F. The characteristic feature is a rapid, severe anemia of the pernicious type. The number of red cells may fall to 1,000,000 or less in three or four days; usually, however, this process takes one or two weeks. The blood contains both normoblasts and megaloblasts; at times it may contain all the bizarre types seen in pernicious anemia. There are also changes in the white cells.

Myelocytes and myeloblasts may be present, causing the picture of leukanemia. The blood shows large numbers of bartonellas as a rule.

The clinical picture of Oroya fever is a distressing one. The patient suffers severe pain in the muscles and joints and has nausea and vomiting. Delirium and coma follow, and death may occur within a few weeks after the onset of fever. The mortality rate is estimated to be from 30 to 90 per cent, an average being about 40 per cent.

Verruga Peruana.—The lesions of the benign type of Carrion's disease, verruga peruana, are of special interest to the dermatologist, as they are unlike those of any other disease, with which I am familiar. The incubation period is probably the same as that of Oroya fever and is followed with (1) a stage of invasion and (2) an eruptive stage.

The stage of invasion lasts approximately three months and is accompanied with a mild fever, usually of the intermittent or tertian type, and with simple anemia, gastrointestinal disturbances and more or less pain in the muscles and joints. The blood may or may not show the presence of bartonellas. The invasive stage ends with the appearance of the eruption and the rapid disappearance of constitutional symptoms. The patient is then on the road to recovery.

The eruption of verruga is of two types: (1) miliary (the common cutaneous type) and (2) nodular (the comparatively rare, subcutaneous type). The lesions of the miliary eruption closely resemble angiomas accompanying senility, pyogenic granulomas or those of generalized sarcomatosis. The lesions begin as hard, shotlike, pinhead-sized papules, some of which enlarge to the size of a split pea. They appear in crops and eventually soften, becoming covered with blood crusts, which show their great vascularity. All the papules are some shade of red, and usually all are discrete (fig. 4). The eruption lasts four to five months or more and eventually disappears, leaving no permanent trace. In extremely rare cases there may be a local recurrence.

The nodular type of eruption occurs in the subcutaneous tissue, the lesions often being felt before they are visible. A rare variety of this type is called *mula,* from its resemblance to a disease in mules. The lesions may become as large as a hen's egg or a small apple. When traumatized, they bleed severely. Death may even occur from hemorrhage.

Thus far no curative remedy has been discovered. Transfusions have been of no avail. Prophylaxis is all-important: Precautions must be taken, when spending the night in infected ravines, not to be bitten by sandflies.

My observations on Carrion's disease are based on experience in Peru in 1934, at a time when the disease was thought to be confined to that country. In 1936 a peculiar disease with a high mortality rate appeared in the southern part of Colombia, and in 1939 Patino-Camargo

proved it to be a form of Carrion's disease. In the following years, from 1940 to 1943, a total of 2,241 cases were recorded, with the fatality rate of 24.8 per cent gradually lowering to 5.5 per cent. The disease has also been seen in Ecuador and Guatemala.

During World War II, 6 cases of Carrion's disease were reported in personnel of the Navy and Marine Corps. The information given me did not state definitely which type was diagnosed.

LEPROSY

While leprosy is not strictly a tropical disease, at least two thirds of the cases originate in moist, hot climates. Space will not allow

Fig. 4.—Carrion's disease (verruga peruana type). Profuse papular eruption with redness present in all the lesions in varying amounts.

mention of more than three features, namely the new classification proposed at the recent International Congress of Leprosy, the results of treatment with the sulfone drugs and the number of members of the United States armed forces who have contracted leprosy in the last three wars.

The Committee on Classification and Nomenclature at the International Congress of Leprosy,[7] which met April 3 to 11, 1948 at Habana, Cuba, proposed that the classic division of leprosy into two

7. Report of the Committee on Classification and Nomenclature, International Congress of Leprosy, Habana, April 3-11, 1948.

types be recognized: "lepromatous" (malignant, symbol "L") and "tuberculoid" (benign, symbol "T"); examples are shown in figure 5. In addition, it was proposed that recognition be given to a type less distinctive, less stable and less certain with respect to evolution and that this type be designated "indeterminate" (indifferent, symbol "I"). The characteristics of the three classes are as follows:

The lepromatous type has a minimal resistance to bacilli; they are constantly present in large numbers and have a tendency to form globi. Characteristic clinical manifestations occur in the skin, mucous

Fig. 5.—Leprosy. Shorter girl, aged 8, shows lepromatous type of three years' duration; other, aged 12, shows tuberculoid type of ten years' duration.

membranes and/or the peripheral nerves, and the reaction to lepromin is negative. The lesions are of the pathognomonic granular type. This type is infectious or "open."

The tuberculoid type has a high resistance to bacilli and shows few or no bacilli except in reactional states. It has characteristic clinical manifestations and gives a positive lepromin reaction in a high percentage of cases. Tuberculoid, granulomatous structure is nearly always present in the active lesions. This type has a tendency to spontaneous regression and is usually noninfectious, or "closed."

The indeterminate type has a variable resistance to bacilli; the clinical manifestations appear chiefly in the skin and nerves. The cutaneous lesions are usually flat macules, which are hypochromic or erythematous. No bacilli, or only a few, are present. The lepromin reaction is usually negative or moderately positive, and the histologic picture shows simple inflammation. Stability is less than in the other types: The disease has a variable tendency to persistance, regression or transformation into one of the first two types. This type is usually noninfectious.

One of three popular sulfone preparations, promin® (sodium p, p′ diaminodiphenylsulfone-N,N′-didextrose sulfonate) has been used at the National Leprosarium at Carville, La., since March 1941. The drug has been given intravenously in daily doses gradually increased from 1 to 5 Gm. Principally patients with advanced cases of the lepromatous type have been treated. Improvement usually begins after six months and is progressive and in proportion to the intensity and duration of the treatment. Improvement was noted in 25 per cent of patients after six months, in 50 per cent after one year, in 75 per cent after two years and in almost 100 per cent after three years. Nodules become absorbed, oral and nasal lesions and ulcerations heal, laryngitis and ocular lesions improve and febrile reactions cease. The need for tracheatomy disappears. The proportion of positive bacteriologic reactions steadily declines; it was reported to be under 50 per cent at the end of four years of treatment.

Diasone® (disodium formaldehyde sulfoxylate diaminodiphenylsulfone) and promizole® (4, 2′-diaminophenyl-5′-thiazolylsulfone) have the advantage of oral administration but have not been used so long as promin® and are more expensive. Results of treatment with them have, however, been similar. In his last-published report, the late Dr. Faget told in detail why chaulmoogra oil was replaced by sulfone preparations at Carville.[8]

In their article on leprosy in veterans, Aycock and Gordon[9] stated that 32 veterans of the Spanish-American War, were admitted to the United States Marine Hospital at Carville from 1921 to 1940. Of this number, 30 had served in endemic areas, mostly in the Philippine Islands, and the remaining 2 had come from endemic areas in Louisiana and Texas.

Fifty-one veterans of World War I, only 6 of whom had seen active service in areas where leprosy was endemic, were admitted to

8. Faget, G. H.: Chemotherapy of Leprosy, Internat. J. Leprosy **15**:7-14 (Jan.-March) 1947; abstracted, Trop. Dis. Bull. **44**:727-728 (Aug.) 1947.

9. Aycock, W. L., and Gordon, J. W.: Leprosy in Veterans of American Wars, Am. J. M. Sc. **214**:329-339 (Sept.) 1947; abstracted, Trop. Dis. Bull. **45**: 186-187 (Feb.) 1948.

Carville. Of 33 born in the United States, all came from southern states where the disease is endemic.

The data given to me on members of the United States Army in World War II show only 22 cases of leprosy in veterans. That this number will be increased in the future is unfortunately true, owing to the long incubation period of the disease.

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ECZEMATOUS AND PUSTULAR ERUPTIONS OF THE HANDS

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ONE OF the commonest groups of diseases of the skin, and one which has proved to be a bane to the postgraduate student in dermatology and has taxed the diagnostic skill of the practicing dermatologist, is the eczematous and pustular eruptions of the hands. The purpose of this article is to arrange the data on these eruptions in a schematic form, for use as a guide. The tables also list causes, clinical attributes and therapy. Dermatologic entities such as scabies, atopic dermatitis, erythema multiforme, syphilis and herpes, which usually involve other areas of the skin as well as the hands are, of course, not considered in this classification.

Acute eruptions
- Common types
  1. Eczematous contact type dermatitis (allergic)
  2. Eczematous dermatitis due to primary irritants
     (*a*) "Housewife's eczema"
  3. Miliaria
  4. Trichophytid
- **Infrequent types**
  1. Primary fungous infections
     (*a*) Moniliasis
     (*b*) Trichophytosis
  2. Streptococcic acrodermatitis

Chronic eruptions
- Frequent types
  1. Chronic fissured eczema
  2. Eruptions resulting from sensitization to foods or drugs
  3. Eruptions resulting from sensitization to pyogen
  4. Nummular eczema
- Infrequent types
  1. Acrodermatitis perstans (dermatitis repens)
  2. Pustular psoriasis
  3. Pustular bacterid
  4. Pompholyx(?) (endogenous intoxications)

CONCLUSION

Despite this simplification, the diagnosis and management of eruptions of the hands is still difficult when, as is often the case, multiple

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	Mechanism	Clinical Attributes	Distribution	Significant Laboratory Findings	Therapy
I. Acute: A. Common Types					
1. Eczematous contact-type dermatitis (allergic)	Acquired altered reactivity resulting from exposure to contactants and manifested on reexposure to these contactants; water-soluble or oil-soluble nonprotein compounds, e. g., plants, dyes, leather, wool or medicaments	May be occupational or nonoccupational Not sharply demarcated Moderately pruritic Classic picture of eczema: erythema, edema, papules, vesicles, oozing and crusting	Unilateral or bilateral Dorsa of fingers and hands; palms not involved Lesions tend to develop beyond sites contacted	Positive reaction to patch test	1. Elimination or avoidance of contact with eliciting agents 2. Symptomatic treatment 3. Change in occupation if necessary
2. Eczematous dermatitis due to primary irritants	Reaction to contact with caustics, acids or dye intermediates Reaction depends on intensity or quantity of contact and duration of contact	Usually due to occupational or industrial exposure Classic picture of eczematization	Palms and dorsa Only contacted sites involved		1. Minimizing of contact with primary irritants 2. Use of protective gloves 3. Use of protective ointments
(*a*) "Housewife's eczema"	Combined effect of immersion in water and irritant action of cleansers, soaps, powders or bleaches	Affects housewives, soda fountain workers			
3. Miliaria	Reaction to hot weather, friction, excessive sweating or emotional difficulties Faulty keratinization and occlusion of pores, with sweat retained in ducts a factor	Sudden onsets and spontaneous remissions Burning, pricking and itching Red or pink, pinhead-sized, conical papules or vesicles Discrete or aggregated tense vesicles	Shafts of fingers, especially lateral margins; hypothenar areas	Positive reaction to quinizarin (Guttmann, L.: Proc. Roy. Soc. Med. **35**:77 [Dec.] 1941)	1. Avoidance of heat and overexertion 2. Application of cool compresses 3. Application of cooling keratolytic tinctures or lotions
4. Trichophytid	Dissemination of fungi and/or products from primary focus on feet to previously sensitized sites on hands	Lesions appearing in crops Variable degree of pruritus Discrete vesicles composed of sago-like grains Spontaneous regression following appropriate management of primary focus	Bilateral Usually starts on sides of fingers, spreading to palms	Fungi seldom found in lesions on hands, but present in scrapings and cultures from feet Positive reaction to trichophytin test	1. Symptomatic prescription for hands with specific fungicidal attack on primary focus (Symptoms on hands clear spontaneously when primary foci are appropriately treated)
B. Infrequent Types					
1. Primary fungous infections (*a*) Moniliasis	Sensitization to Candida albicans Improper drying of hands and overuse of soap	Picture of erosio interdigitalis blastomycetica: soggy, whitish, erythematous, scaly and erosive patches	Interdigital areas, usually between ring and middle fingers	(*a*) Presence of C. albicans demonstrated by direct examination and culture	1. Avoidance of soap which lessens alkali-neutralizing power of skin and affords alkaline pabulum for C. albicans
(*b*) Trichophytosis	Sensitization to superficial fungi (usually Trichophyton purpureum)	Picture of tinea corporis	Palms, dorsa, fingers and nails	(*b*) Presence of fungus demonstrated by direct examination and culture	2. Application of gentian violet and Castellani's paint* 3. Application of propionic and undecylenic acid creams

* Castellani's paint contains saturated alcoholic solution of basic fuchsin, 10 cc.; aqueous solution of 5 per cent phenol, 100 cc.; boric acid, 1 Gm.; acetone, 5 cc., and resorcinol, 10 Gm.

2. Streptococcic acrodermatitis (Mitchell, J. H.: Arch. Dermat. & Syph. **19**: 659 [April] 1929)	Streptococcic infection	Vesicular and crusted lesions (impetiginous) with tendency to erosion and exudation; of short duration	Bilateral Fingers, palms and dorsa	Presence of streptococci in serum from unruptured vesicle	Parenteral administration of penicillin Application of compresses of tyrothricin
		II. Chronic: A. Frequent Types			
1. Chronic fissured eczema	Defatting or degreasing action of alkalis or solvents	Red, dry, scaly, thickened, fissured and lichenified skin Usually occupational in origin— Workers handling turpentine, kerosene or strong soap	Palms and dorsa		1. Minimizing of contact with alkalis and solvents 2. Use of protective gloves 3. Greasing of hands with animal or vegetable fat
2. Eruptions resulting from sensitization to food or drugs (Flood, J. M., and Perry, D. J.: J. Invest. Dermat. **7**: 309 [Dec.] 1946. Rowe, A. H.: Arch. Dermat. & Syph. **54**: 683 [Dec.] 1946. Carpenter, C. C.: J. M. Soc. New Jersey **42**: 262 [Aug.] 1945)	Sensitization to foods, e. g., milk, wheat, eggs, pork, cheese or citrus fruits Sensitization to drugs, e.g., ephedrine, ("mecholyl chloride"), penicillin or sulfonamide drugs	Prompt exacerbation and remission of lesions after administration and elimination of allergens (Results of elimination diets most valuable; Food diary)	Shafts of fingers and hypothenar and thenar eminences		1. Removal of foods from diet 2. Discontinuation of drugs
3. Eruptions resulting from sensitization to pyogen	1. Sensitization of skin to streptococci or staphylococci in situ Alteration in host-bacteria relation (Lane, C. G., and others: J. A. M. A. **128**: 987 [Aug. 4] 1945) 2. Sensitization due to synergy of toxins of streptococci or staphylococci and keratin (Hopkins, H. H., and Burky, E. L.: Arch. Dermat. & Syph. **49**: 124 [Feb.] 1944)	1. Picture of infectious eczematoid dermatitis An entity developing after infected trauma or superimposed on some primary inciting factor (Lane, C. G., and others: J. A. M. A. **128**: 987 [Aug. 4] 1945)	May be localized to hands and may involve other parts of body	Positive reaction to intracutaneous inoculation with staphylococcus ambotoxoid and staphylococcus toxin	1. Desensitization with staphylococcus ambotoxoid or staphylococcus toxin 2. Topical prescriptions, ammoniated mercury
4. Nummular eczema	1. Sensitization to viruses (?) 2. Vitamin deficiency (?)	Sharply demarcated, coin-shaped lesions with central clearing and Grouped, pinhead-sized papules and vesicles in periphery vesicles Thin-walled vesicles, rupturing readily, then oozing and crusting Lesions usually disappear in summer and reappear in winter	Dorsa of hands with frequent involvement of extensor surface of forearms	No fungi or organisms demonstrated in lesions	1. Spraying with ethyl chloride 2. Parenteral administration of crude liver extract 3. Administration of vitamin A (100,000 units per day) 4. Application of antiparasitic lotions or pastes

Classification of the Eczematous and Pustular Eruptions—Continued

	Mechanism	Clinical Attributes	Distribution	Significant Laboratory Findings	Therapy
B. Infrequent Types					
1. Acrodermatitis perstans (dermatitis repens)	Probably microbic	Often initiated by an injury or paronychia; slowly progressive Initial lesions: vesicles, bullae and pustules, progressing to patches with oozing centers and undermined borders	Usually begins on one finger near nail, spreading slowly to palm and other fingers Usually unilateral	Presence of cocci in pustules	Débridement, administration of antibiotics and toxoid Local applications of potassium permanganate and tyrothricin
2. Pustular psoriasis	1. Pustulation (essential part of psoriatic process) 2. Entity (controversial)	Reddened patches with pinhead-sized intraepidermic pustules Lesions dry and form minute, brownish scabs	Thenar eminences, arch areas and heels	Histopathologic picture of psoriasis Pustules sterile	Usual treatment for psoriasis
3. Pustular bacterid (Andrews, G. C., and Machachek, G. F.: Arch. Dermat. & Syph. **32**: 837 [Dec.] 1935. Barber, H. W.: Brit. J. Dermat. **45**: 113, 1933)	Dissemination of bacterial products from distant foci of infection to sensitized skin sites	Chronic course Eczematous patches studded with pustules No response to topical remedies	Bilaterally symmetric Affects most often the soles, but also the palms	Pustules nearly always sterile Leukocyte count rises during pustular outbreaks Positive reaction to intracutaneous injections of streptococci and staphylococci	Removal of primary foci of infection in teeth or tonsils
4. Pompholyx (?) (endogenous intoxications)	1. Absorption of toxins from menses or gastrointestinal tract 2. Infection with endoparasitic bacilli (Benedek, T.: Indust. Med. **16**: 344 [July] 1947) 3. Action of endogenous toxin on skin previously prepared by occupational exposure (Blaisdell, J. H., and Swartz, J. H. H.: Arch. Dermat. & Syph. **51**: 365 [June] 1945) 4. Psychosomatic	1. Reappearance of lesions at regular intervals (26-28 days) 2. Eruptions preceded by burning and itching for 24 hours Absence of preeruptive erythema	Palms, sides of fingers and interdigital folds		1. Desensitization with premenstrual autoserum 2. Vaccine of endoparasitic bacillus 3. Local application of soothing, drying antiseptics 4. Psychosomatic treatment

etiologic factors are present. One must then understand the synergistic interplay between such factors as contact, fungus, pyogen, virus and food allergy and those of emotion, sweat, soap and water. After this, as Sulzberger [1] stated, "Cure can be effected . . . by simply striking out one of the links of the chain of causes."

1715 Pine Street.

1. Sulzberger, M., in discussion on Lane, C. G.; Rockwood, E. M.; Sawyer, C. S., and Blank, I. H.: Dermatoses of the Hands, J. A. M. A. **128**:987 (Aug. 4) 1945.

NECROBIOSIS LIPOIDICA (DIABETICORUM?)

A Histologic Study and Comparison with Granuloma Annulare

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CONTROVERSY still exists concerning the pathogenesis of necrobiosis lipoidica (diabeticorum?) [1] and the relationship of this disease to granuloma annulare. The purpose in undertaking this study was to glean some information which might further knowledge regarding these problems. The material consisted of histologic sections obtained in 41 cases of necrobiosis lipoidica diabeticorum and 33 cases of granuloma annulare collected since 1934 at the University of Minnesota.

The clinical features of both diseases are so well known that they will not be discussed in this paper. Certainly the differences are so striking in most cases that differentiation offers little difficulty. Among the articles which cover various aspects of necrobiosis lipoidica diabeticorum in more or less detail are those by Oppenheim [1a]; Urbach [2]; Balbi [3]; Zeisler and Caro [4]; Michelson and Laymon [5] and, more recently, Gottron [6]; Boldt [7]; Hildebrand, Montgomery and Rynearson,[8] and

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1. (Diabeticorum?) is used because diabetes mellitus, while present in most cases of necrobiosis lipoidica, is absent in a sufficiently large number to provoke discussion of this feature.

1a. Oppenheim, M.: Ueber eine bisher nicht beschriebene, mit eigentümlicher lipoider Degeneration der Elastica und des Bindegewebes einhergehende chronische Dermatose bei Diabetes mellitus (Dermatitis atrophicans lipoides diabetica), Arch. f. Dermat. u. Syph. **166**:576-583, 1932.

2. Urbach, E.: Eine neue diabetische Stoffwechseldermatose: Necrobiosis lipoidica diabeticorum, Arch. f. Dermat. u. Syph. **166**:273-285, 1932.

3. Balbi, E.: Ricerche intorno alla patogenesi della necrobiosis lipoidica diabeticorum Urbach-Oppenheim, Gior. ital. di dermat. e sif. **74**:14-43 (Feb.) 1933.

4. Zeisler, E. P., and Caro, M. R.: Necrobiosis Lipoidica Diabeticorum (Urbach), Arch. Dermat. & Syph. **29**:167-169 (Jan.) 1934.

5. Michelson, H. E., and Laymon, C. W.: (*a*) Necrobiosis Lipoidica Diabeticorum, Arch. Dermat. & Syph. **35**:1130-1136 (June) 1937; (*b*) Necrobiosis Lipoidica Diabeticorum (Urbach), J. A. M. A. **103**:163-169 (July 21) 1934.

6. Gottron, H.: Dermatitis atrophicans lipoides diabetika, Zentralbl. f. Haut- u. Geschlechtskr. **43**:47 (March) 1933.

Ellis and Kirby-Smith[9]. Detailed discussions of granuloma annulare include those by Little,[10] Arndt,[11] Halliwell and Ingram,[12] Goodman and Ketron,[13] Boldt,[14] Prunty and Montgomery[15] and Bolgert.[16]

In this paper, the histologic aspects of the two diseases, including necrobiosis, infiltrate, changes in blood vessels and special features, will be analyzed and compared. Oppenheim,[1a] who first described necrobiosis lipoidica diabeticorum, stated that the chief histologic feature was a fatty degeneration of the connective tissues, such as Kreibich[17] described in sailors' skin and in cutis rhomboidalis nuchae. He emphasized the fact that the microscopic changes in necrobiosis lipoidica diabeticorum were entirely different from those in xanthoma diabeticorum, for there was a complete absence of xanthoma and of giant cells in the former.

In his publications and in discussions before meetings of medical societies, Oppenheim maintained that the degeneration was brought about by circulating toxic substances which were an accompaniment of the diabetes and which by their local action caused a colloidal-chemical change in the tissues. Although his histologic studies showed no amyloid, colloid, hyaline or mucinous degenerations, he deducted from his study of sections stained by the Van Gieson method that there was some specific change in the connective tissue. In sections stained with sudan III he observed intracellular and extracellular lipid droplets.

Urbach[2] stated the opinion that the condition was a necrobiosis of the connective tissue, followed by imbibition of lipids. He stated, in objection to Oppenheim's views, that the lipid degeneration described

7. Boldt, A.: Zur Kenntnis der Necrobiosis lipoidica ("diabeticorum"), Arch. f. Dermat. u. Syph. **179**:74-119, 1939.

8. Hildebrand, A. G.; Montgomery, H., and Rynearson, E. H.: Necrobiosis Lipoidica Diabeticorum, Arch. Int. Med. **66**:851-878 (Oct.) 1940.

9. Ellis, F. A., and Kirby-Smith, H.: Necrobiosis Lipoidica and Granuloma Annulare, Arch. Dermat. & Syph. **45**:40-60 (Jan.) 1942.

10. Little, E. G.: Granuloma Annulare, Brit. J. Dermat. **20**:213-229 (July) 1908.

11. Arndt, G.: Zur Kenntnis des Granuloma annulare (Radcliffe Crocker), Arch. f. Dermat. u. Syph. **108**:229-260, 1911.

12. Haliwell, E. O., and Ingram, J. T.: Granuloma Annulare, Brit. J. Dermat. **47**:319-340 (Aug.-Sept.) 1935.

13. Goodman, M. H., and Ketron, L. W.: Granuloma Annulare, Arch. Dermat. & Syph. **33**:473-494 (March) 1936.

14. Boldt, A.: Beitrag zur Klinik und Ätiologie des Granuloma annulare, Arch. f. Dermat. u. Syph. **179**:603-610, 1939.

15. Prunty, F. C., and Montgomery, H.: Granuloma Annulare, Arch. Dermat. & Syph. **46**:394-413 (Sept.) 1942.

16. Bolgert, M.: A propos de la pathologie du granuloma annulare, Ann. de dermat. et syph. **4**:137-147, 1944.

17. Kreibich, cited by Oppenheim.[1a]

by Kreibich about thirty-five years before was in no way analogous to the process that occurs in necrobiosis lipoidica diabeticorum. The sudanophilia that Kreibich noted was limited exclusively to the swollen, fragmented elastic fibers, while in necrobiosis, Urbach stated, the chief changes appeared in the connective tissue, with the elastic fibers for the most part completely absent in the necrobiotic areas.

As a further objection to the theory of local degeneration as an explanation of the pathogenesis, Urbach cited the belief, prevalent among pathologists, that it is improbable, but not indisputable, that fat can originate in cell protein. The accepted view is that the lipid in such degenerations comes from the blood or the lymph stream and not from the cells themselves.

In support of his own ideas regarding the pathogenesis, Urbach claimed that the arrangement of the lipid droplets in chains and clusters made it probable that they had come from the blood stream, and cited the current belief that all necrotic tissue masses of the type found in necrobiosis lipoidica diabeticorum attract substances circulating in the blood. Such a state exists in cases of poorly controlled diabetes, as illustrated by the presence of hyperlipemia. Hence the necrotic masses take up the circulating fatty substances.

Urbach stated the opinion that certain toxins due to diabetes cause a severe disturbance in the vessels of the corium, leading to necrobiosis, as evidenced by loss of cells and nuclei, homogenization of the connective tissue and deposition of calcium salts. These primarily necrobiotic tissues then imbibe lipid substances, which are often pathologically increased in the blood of diabetic patients.

HISTOLOGIC OBSERVATIONS

Necrobiosis Lipoidica Diabeticorum.—Several sections were made in each of our cases of necrobiosis lipoidica diabeticorum, and, with a few exceptions, were stained with hematoxylin and eosin, with sudan III and with the methods of Weigert and Van Gieson. In addition, attempts were made to demonstrate mucin in sections from 2 cases, with the Mayer mucicarmine and thionine methods, but no mucin was found. In some sections a modification of the sudan III method suggested by Cecil Jackson[18] was used but offered no advantages over the usual sudan III method. Some sections were stained with potassium ferrocyanide to demonstrate hemosiderin.

Necrobiosis: The most striking histologic feature of necrobiosis lipoidica diabeticorum was the peculiar change in the connective tissue, which occurred most frequently in broad sheets or bands extending transversely throughout the cutis (fig. 1). The areas of necrobiosis, however, did not invariably appear in bands; in many instances, smaller, more circumscribed, foci could be seen, especially about the blood vessels.

18. Jackson, C.: An Improved Method of Staining Lipids (Acetic Carbol Sudan), Onderstepoort J. Vet. Sc. **19**:169-176 (Jan.-April) 1944.

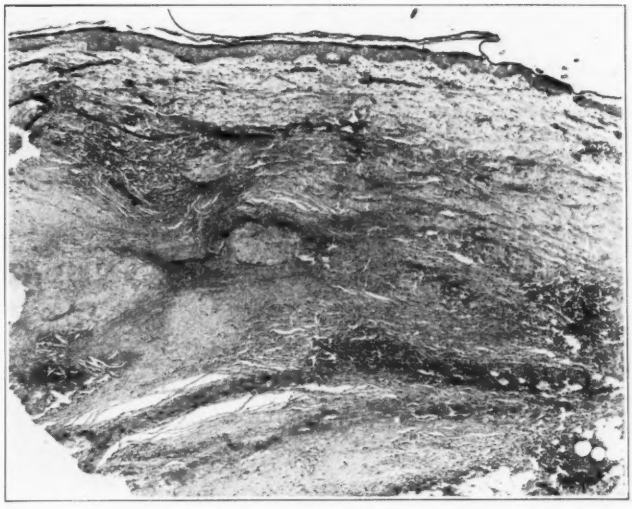

Fig. 1.—Necrobiosis lipoidica diabeticorum: Broad sheets of necrobiotic tissue in the middle and deep portions of the cutis.

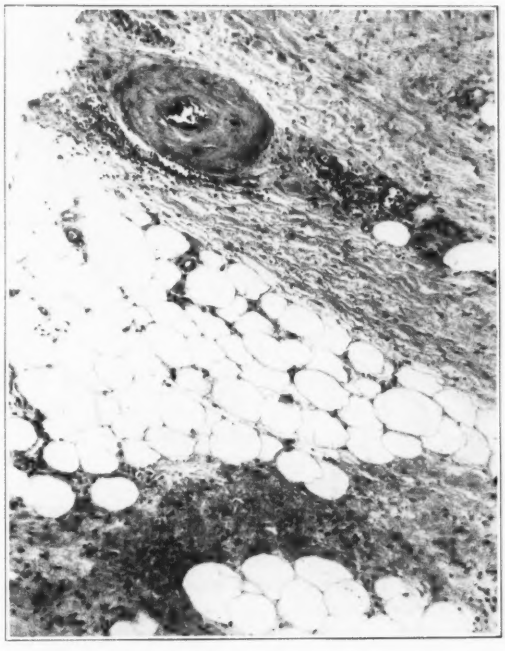

Fig. 2.—Necrobiosis lipoidica diabeticorum: Replacement of fat in the hypodermis. Note obliterative changes in the blood vessel.

The depth of the necrobiotic areas was subject to considerable variation. In some cases this change might be relatively superficial, being confined to the upper portions of the cutis, while in other instances it might extend throughout the entire cutis into the subcutis. The middle and deeper parts of the cutis were more frequently affected than the papillary portion. In some of the sections examined the inflammatory process extended into the hypodermis, so that there was actual replacement of fat, not unlike that which characterizes erythema induratum (fig. 2). In that disease, however, the degree of inflammation is much more intense.

The degree of necrobiosis was variable. The most characteristic changes were seen in sections stained with hematoxylin and eosin. With this stain the necrobiotic areas presented an unusual pallor, which gave the tissues a parboiled appearance. In these affected zones, the connective tissue was homogenized and

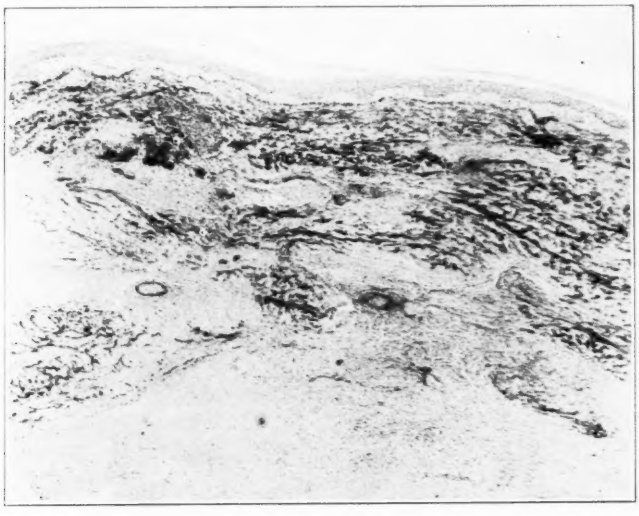

Fig. 3.—Necrobiosis lipoidica diabeticorum: Elastic tissue, showing almost complete loss of the elastic fibres in the necrobiotic and infiltrated areas. Note preservation of the elastic tissue in the obliterated blood vessel.

fragmented, and there was either diminution or complete disappearance of nuclei, depending on the severity of the process in the individual case. In a few instances the preexisting nuclei were represented by masses of debris (chromatin dust) situated in the center of a necrobiotic area. Total necrosis, however, was not observed.

Appropriate stains showed that the elastic tissue was severely damaged in the necrobiotic areas and at the sites of heavy infiltration. For the most part the elastic fibers had disappeared completely (fig. 3), although clumped and fragmented remnants could be seen in some sections (fig. 4).

The Van Gieson method was of value in demonstrating changes in the connective tissue. However, in some sections which presented extensive areas of homogenization when stained with hematoxylin and eosin, the Van Gieson method

demonstrated surprisingly large numbers of connective tissue fibers which were tinctorially normal. The ratio of degenerated to normal fibers varied in different cases, so that some necrobiotic areas appeared pink, rather than the normal red of healthy connective tissue, whereas others assumed a yellow hue.

Infiltrate: Both the intensity and the arrangement of the infiltrate varied considerably in different cases of necrobiosis lipoidica diabeticorum. Most characteristic was its peripheral arrangement, as a husk about the necrobiotic areas. In certain places it was seen also as perivascular mantles. In some cases the amount of infiltrate was surprisingly slight, especially in sections presenting extensive zones of necrobiosis. It was of a chronic inflammatory nature, being constituted for the most part of lymphocytes, histiocytes, epithelioid cells and fibroblasts, in varying proportions.

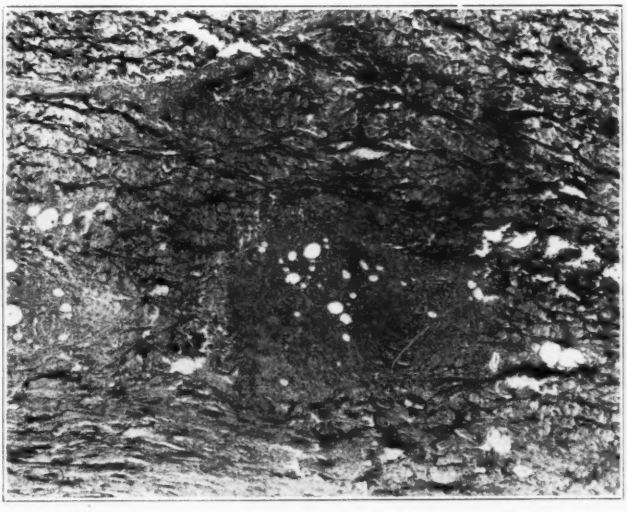

Fig. 4.—Necrobiosis lipoidica diabeticorum: Elastic tissue, showing loss of the fibers in a necrobiotic focus.

In some of our cases the preponderance of epithelioid cells was so great that a tuberculoid structure was produced, simulating the picture of sarcoid. Giant cells were the exception rather than the rule in our cases, but in a few sections they were rather numerous. No special arrangement was noted, and both the Langhans and the foreign body type were observed. In a few other cases fibroblasts dominated the scene to such an extent that the histologic picture mimicked that of subepidermal fibrosis. In other cases the infiltrate was almost purely lymphocytic. Palisading was infrequent. Plasma cells were occasionally noted but were of no special significance. In a few sections eosinophils were present in large numbers, whereas in others they were completely absent. Neutrophils were absent except in a few cases in which there was ulceration. Hemorrhage of varying degree occurred in several cases.

Changes in Blood Vessels: Dilatation of the capillaries and an increase in their number in the upper parts of the cutis occurred in a high percentage of cases. The most striking changes, however, were obliterative and involved the smaller

vessels in the deeper portions of the cutis. Thickening of the walls of the vessels, sometimes almost to the point of complete closure, was seen frequently (fig. 5). Dr. B. J. Clausen, of the department of pathology, examined some of our sections, with special reference to the changes in the vessels. He stated that the most striking feature was fibrosis and thickening of the media and that he regarded the granulomatous changes near and around some of the vessels as those of periarteritis.

Special Features: The most striking special feature of necrobiosis lipoidica diabeticorum was the presence of varying amounts of lipids in the areas of necrobiosis. In sections stained with sudan III the lipids appeared brownish red, in contrast to the brighter red of neutral fat, and seemed to be deposited both between and within the fibers. Lipids were not seen in all necrobiotic areas. The presence of lipids could be demonstrated in the infiltrate and about the blood

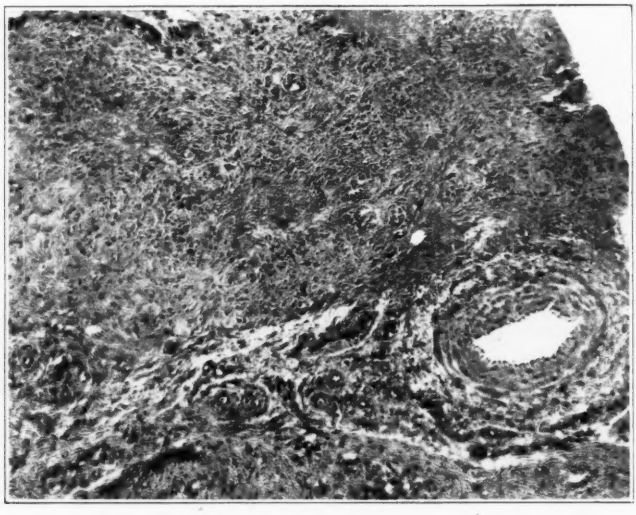

Fig. 5.—Necrobiosis lipoidica diabeticorum: Thickening of wall of a blood vessel in the deep cutis, with adjacent areas of necrobiosis and fibroplastic proliferation.

vessels. They appeared usually as extracellular deposits, although occasionally one saw histiocytes laden with fat, which resembled foam cells. Fat was also present in giant cells. The lipids rarely showed double refraction. We made no effort in this study to determine the types of lipids by histochemical methods; such methods are of questionable value in differentiating lipids which may occur abnormally in tissues.

Deposits of hemosiderin occurred rather frequently in necrobiosis lipoidica diabeticorum, and the presence of calcium could occasionally be demonstrated.

Epidermal changes were usually insignificant or lacking entirely. The epidermis might be normal or atrophic, but it was never acanthotic. Ulceration, which was occesionally present, was of diagnostic value, since it never occurs in granuloma annulare. If there is no ulceration, the stratum corneum is either normal or hyperkeratotic.

Granuloma Annulare.—Careful examination of sections from our cases of necrobiosis lipoidica diabeticorum and comparison with sections from cases of granuloma annulare left not the slightest doubt that the clinical features of the two diseases are far more important than the histologic in making a differentiation.

As in necrobiosis lipoidica diabeticorum, the most important histologic changes in granuloma annulare occurred in the cutis, and the epidermal changes were usually insignificant. Exceptionally, however, acanthosis was seen on the lesions of granuloma annulare, whereas it was absent in necrobiosis lipoidica diabeticorum. The papillary portion of the cutis was usually unaffected except for moderate dilatation of the capillaries, which, however, was not seen so frequently as in necrobiosis lipoidica diabeticorum. An increase in the number of capillaries in the upper part of the cutis was not noted in cases of granuloma annulare.

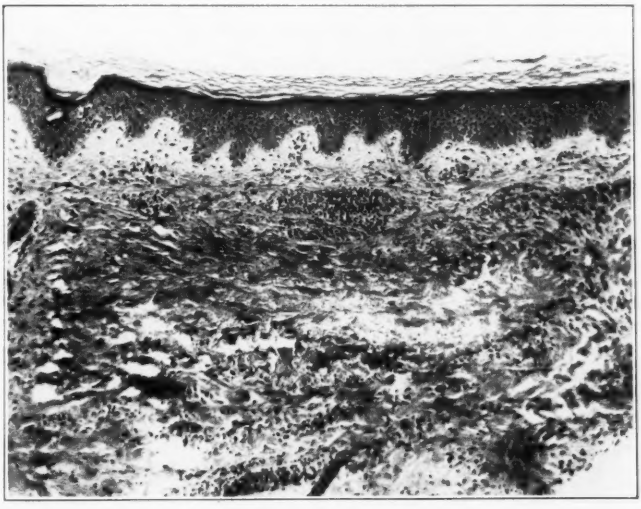

Fig. 6.—Granuloma annulare: Characteristic appearance, with ellipsoidal zone of necrosis and radially arranged infiltrate in the middle portion of the cutis.

This point alone, however, is insufficient to make the differentiation of the two diseases.

The important changes occur most frequently in the middle parts of the cutis, although in some of our sections involvement extended down to the subcutis. The general location of the changes did not offer in itself any good means of distinguishing granuloma annulare from necrobiosis lipoidica diabeticorum, although it was our impression that the changes were not so deep in most cases of granuloma annulare.

The most characteristic lesion in granuloma annulare consists of a fairly well demarcated, spherical or ellipsoid area of necrobiotic connective tissue surrounded by a zone of infiltrate arranged in a stellate, radial or palisade formation and made up of lymphocytes, fibroblasts and epithelioid cells, in varying proportions (fig. 6). This feature (necrosis combined with palisading of infiltrate) is more consistent in granuloma annulare and less subject to the rather wide variations,

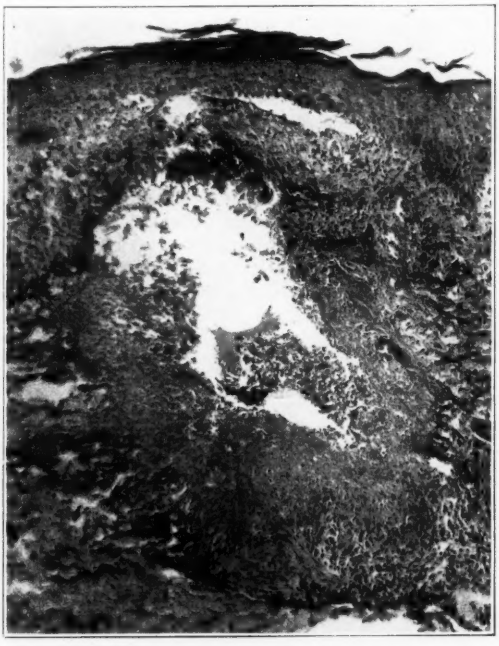

Fig. 7.—Granuloma annulare: Well developed palisade formation of infiltrate.

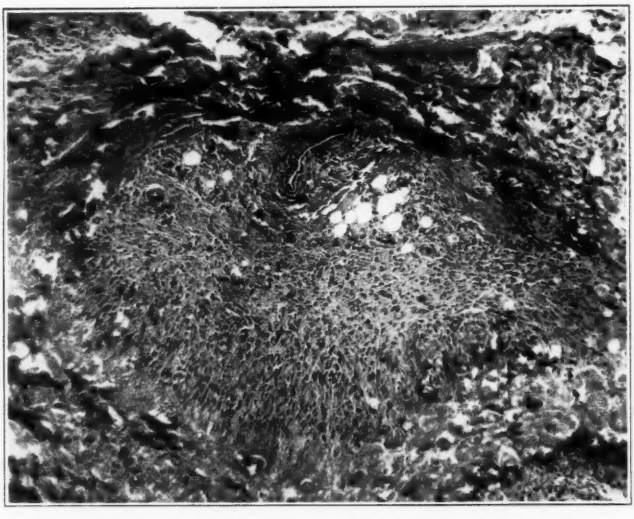

Fig. 8.—Granuloma annulare: Sequestral necrosis, with the area of disintegration of the tissues surrounded by typically arranged infiltrate.

previously described, in necrobiosis lipoidica diabeticorum. Almost without exception the zones of coagulation in cases of granuloma annulare were more sharply circumscribed than those in cases of necrobiosis lipoidica diabeticorum (fig. 7), and there was a more intense degree of alteration of the connective tissue in most cases of the former. In a few sections there was complete sequestration necrosis, with disintegration of the tissues leaving large spaces in the section surrounded by the typical radially arranged infiltrate (fig. 8).

Despite the fact that the histologic picture of granuloma annulare is, in general, more constant than that in necrobiosis lipoidica diabeticorum, there were many instances in which sections from cases of the one were indistinguishable from those from cases of the other. Sections from a few cases of granuloma annulare were encountered which were characteristic clinically but which showed histologically only edema, mild homogenization and fragmentation of the connective tissue

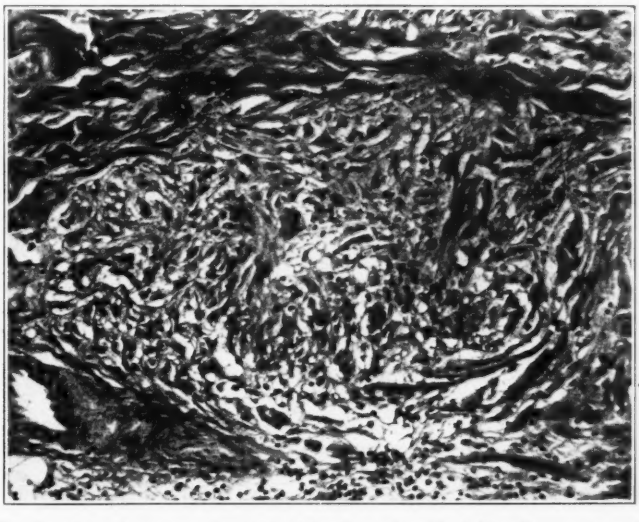

Fig. 9.—Granuloma annulare: Proliferation of epithelioid cells, to the point of simulating a tuberculoid structure.

with separation of the fibers. In these instances the areas of necrosis were either minimal or entirely absent, and the infiltrate was arranged chiefly about the sweat glands. In some sections there was a preponderance of the epithelioid component of the infiltrate to the point of producing a frank tuberculoid structure (fig 9). Giant cells were a rarity and appeared much less frequently than in necrobiosis lipoidica diabeticorum. In some cases there was fibroblastic proliferation simulating the picture of necrobiosis lipoidica diabeticorum.

Diminution, fragmentation or complete disappearance of the elastic tissue was a constant feature in the sections from cases of granuloma annulare and offered no important means of distinguishing the disorder from necrobiosis lipoidica diabeticorum. These changes, varying in degree, were present in the zones of necrosis, as well as in the infiltrated areas.

Hemorrhage was not encountered in any of our cases of granuloma annulare.

Changes in Blood Vessels: The vascular changes in our cases of granuloma annulare were difficult to appraise because of the variations. Obliterative changes and intimal proliferation, such as were relatively frequently seen in cases of necrobiosis lipoidica diabeticorum, could not be found in our cases of granuloma annulare.

It has been suggested, because of the histologic similarity of these two conditions, that staining for fat might afford a means of differentiation. In our experience, it has proved true that the presence of lipids is much more frequent in the lesions of necrobiosis lipoidica diabeticorum, but the presence of lipids most certainly does not rule out a diagnosis of granuloma annulare. Unfortunately, at the time of the beginning of this investigation the tissues from cases of granuloma annulare had been embedded in paraffin, so that staining for fat was impossible. In 3 recent cases, however, deposits of lipids equal in degree to many we have seen in cases of necrobiosis lipoidica diabeticorum were demonstrated.

Sections from 4 cases of granuloma annulare were stained with the Mayer mucicarmine and thionine methods. Although we had hoped that this might give additional aid in the differentiation of the two diseases, as suggested by Prunty and Montgomery,[15] no mucin was found.

COMMENT

As stated previously, we desired first to obtain evidence which would facilitate positive differentiation of necrobiosis lipoidica diabeticorum and granuloma annulare, since we are not of the opinion that the two are variants of the same disease. Secondly, we hoped to gain information which might aid in a better understanding of the pathogenesis of necrobiosis lipoidica diabeticorum.

As to the first point, the actual analysis of the sections from a relatively large number of cases of the two diseases has been discussed in preceding paragraphs, and the differences, as we saw them, have been given. As a result of careful scrutiny of this material, we believe that a histologic differentiation can usually be made with reasonable certainty if one utilizes all the means at one's command, which include ordinary staining with hematoxylin and eosin and special staining for lipids and mucin. In 1942, Ellis and Kirby-Smith,[9] in an excellent, thorough comparative study covering both the clinical and the histologic aspects of the two diseases, stated: "All of the clinical, histologic and histochemical features of necrobiosis lipoidica have at times been associated with granuloma annulare." With this statement we agree, but still we do not feel that this similarity permits the conclusion that the two diseases are one and the same. It is the extremely rare exception, rather than the rule, that sufficient differences (especially clinical) do not exist to permit positive differentiation of the two diseases. Late syphilis, in an occasional case, may be practically identical clinically and histologically with lupus vulgaris; yet in the vast majority of instances there are features which clinch the differential diagnosis. In attempting to establish the unity or duality of questionable diseases, one must base conclusions on the great majority of cases, rather than on

the rare exceptions in which the diseases may closely simulate each other. For many years erythema elevatum diutinum was considered a variant of granuloma annulare, but the tendency in the past decade is against such a concept. Combes and Bluefarb [19] concluded that the two were separate entities, and Lever [20] recently suggested that erythema elevatum diutinum might be related to eosinophilic granuloma of the skin. Even though it were granted that erythema elevatum diutinum and granuloma annulare are variants of the same disease, most cases of the former bear little or no resemblance to necrobiosis lipoidica diabeticorum, so that no additional evidence is forthcoming

Histologic Differences Between Necrobiosis Lipoidica Diabeticorum and Granuloma Annulare

	Necrobiosis Lipoidica Diabeticorum	Granuloma Annulare
Changes in Epidermis	Usually insignificant; epidermis may be atrophic but not acanthotic; ulceration may occur	Usually of no special value in diagnosis; epidermis may be acanthotic; ulceration does not occur
Location of Degenerative Changes	Middle and deep portions of cutis and subcutis	Upper and middle rather than deep portion of cutis in most cases
Areas of Degeneration	More often in sheets or bands; more often less well defined; necrobiotic	More often spherical or ellipsoid; more often sharply marginated; more intense degeneration; actual necrosis occasionally present
Type of Infiltrate	Chronic inflammatory type: lymphocytes, histocytes, fibroblasts and epithelioid cells in varying proportions; giant cells not rare; occasional hemorrhage	No significant differences from necrobiosis lipoidica diabeticorum; giant cells rare; hemorrhage not present
Arrangement of Infiltrate	More diffuse than in granuloma annulare; about necrobiotic areas and vessels; palisading rare	Palisading (radial arrangement) outstanding
Lipids	Present almost without exception in necrobiotic areas	May be present
Changes in Blood Vessels	Intimal proliferation and obliterative changes fairly frequent; increased number and dilatation of capillaries in papillary portion of cutis	Obliterative changes rare; dilatation of vessels

in favor of the view that necrobiosis lipoidica diabeticorum and granuloma annulare are the same.

In brief summary, the histologic differences between necrobiosis lipoidica diabeticorum and granuloma annulare are given in the accompanying table.

The pathogenesis of necrobiosis lipoidica diabeticorum is still debatable. The view that the condition is an "obligatory diabetic dermatosis" must be seriously questioned in view of the fact that approximately 15 per cent of the cases occur in nondiabetic patients. Oppenheim [21]

19. Combes, F. C., and Bluefarb, S. M.: Erythema Elevatum Diutinum: Report of Case, Arch. Dermat. & Syph. **42**:441-446 (Sept.) 1940.

20. Lever, W. F.: Eosinophilic Granuloma of the Skin, Arch. Dermat. & Syph. **55**:194-211 (Feb.) 1947.

21. Oppenheim, M.: Personal communication to the authors.

expressed the belief that in this group there is frequently a history of diabetes in the family or of abnormalities in glucose tolerance. Without question, however, there are cases in which no diabetes has occurred even years after typical lesions of necrobiosis lipoidica have developed. In 1938 Gottron [22] presented his hypothesis that the principal factor in the pathogenesis of necrobiosis lipoidica is an increased irritability of the cutaneous circulation and that a disturbance of the carbohydrate or fat metabolism is not a prime requisite. He stated the opinion that the microscopic picture favored such a theory, i. e., more or less obvious vascular changes, leading to a gradually progressive alteration of the connective tissue. Necrobiosis, rather than complete necrosis, suggests that there is not a complete stasis. The presence of hemorrhage (erythropedesis) and of deposits of hemosiderin signified the possibility of bloody infarction as a part of the process. Gottron's statement agreed with that of Urbach [2] that the necrobiosis was caused by a local disturbance of circulation, but he maintained that the deposit of lipids in the necrobiotic areas was primarily dependent not on a general disturbance of the lipoid metabolism but on the condition of the tissues receiving the lipids. He maintained that the deposit of lipids in necrobiotic tissue was an index not of disturbed metabolism but of the condition of local circulation. Lipid deposits have been found in conditions in which there is no disturbance of lipid metabolism, for example, in gummas, in rheumatic nodules and in gangrenous areas in nondiabetic patients. It has even been possible to identify cholesterol crystals in gangrenous areas in patients with a normal amount of cholesterol in the blood. Gottron compared the deposit of lipids in necrobiosis lipoidica to that of mucin in the skin in myxedema, both being fostered by local changes in the blood vessels. In support of his view, Gottron brought out that the presence of hypercholesteremia, hyperlipemia or a disturbed cholesterol-cholesterol ester quotient was inconstant in cases of necrobiosis lipoidica.

In refutation of Urbach's opinion that toxic products produced the changes in the blood vessels, Gottron cited Thannhauser, who stated that it was his firm belief that toxic intermediate products causing changes in the vessels (such as arteriosclerosis) are unknown in diabetes mellitus. Thannhauser observed that many diabetic persons had vasomotor stigmas (hypotonia, intermittent claudication, dermographism, cutaneous irritability following injections, abnormalties of the optic vessels, hyperhidrosis or a tendency to flushing). Boldt [7] noted that vasomotor instability was common in young diabetic patients, as is arteriosclerosis in older diabetic persons. The location of the

22. Gottron, H.: Zur Kenntnis und Pathogenese der Dermatitis atrophicans lipoides diabetica bzw: Nekrobiosis lipoidica diabetica, Med. Klin. **34**:145-159 (Feb. 4); 190-193 (Feb. 11) 1938.

lesions of necrobiosis lipoidica in the acral parts favors the view that circulatory disturbances constitute an important role in its pathogenesis. Michelson and Laymon,[5b] as early as 1934, expressed the view that necrobiosis lipoidica diabeticorum was more closely related to gangrene than was any other integumentary process in diabetes. This opinion was reached after biopsies were performed on tissues taken at various distances from gangrenous areas in diabetic patients, in an effort to ascertain whether or not tissues adjacent to areas of diabetic gangrene showed necrobiotic foci. They stated that there was sufficient similarity to justify one in considering the processes closely related, the variation being mostly one of degree. Boldt also likened the occurrence of necrobiosis lipoidica in young diabetic patients to that of gangrene in older diabetic patients.

Strictly from the histologic standpoint, our observations are consistent either with the theory of toxic origin, held by Urbach, or with that of vascular changes, held by Grotton and Boldt. All observers have noted the frequent presence of obliterative changes of the vessels in necrobiosis lipoidica, but the microscopic features per se cannot enable one to decide what primarily caused those changes. Certainly, disturbances in the fat or carbohydrate metabolism cannot explain necrobiosis lipoidica in the nondiabetic patient, whereas the theory of vascular disturbance can do so. We could find no significant histologic differences between the lesions of necrobiosis lipoidica in diabetic patients and those in nondiabetic patients, of which there were 4. There are those who believe that vascular stigmatization is an important factor in the pathogenesis of diabetes mellitus itself. Moreover, the demonstration of fat droplets in a certain necrobiotic area does not tell us how the fat arrived at that precise point, or whether it arrived there because of local disturbances or of metabolic ones. As is the case in most diseases, it is impossible even to begin the formulation of a theory of pathogenesis by selecting a single aspect of necrobiosis lipoidica diabeticorum. The disease must be considered in its entirety, and even then in many cases the problem remains unsolved.

SUMMARY AND CONCLUSION

Histologic sections from 41 cases of necrobiosis lipoidica (diabeticorum?) and from 33 cases of granuloma annulare are analyzed and compared. The following conclusions are drawn from the results of the study:

1. The epidermal changes in either disease are usually unimportant in differential diagnosis. The exception is ulceration, which occurs in necrobiosis lipoidica diabeticorum and not in granuloma annulare.

2. The change in the connective tissue is the most significant histologic feature of both diseases. In necrobiosis lipoidica diabeticorum

it is more likely to appear in bands and to be less well defined, while in granuloma annulare it is more often spherical or ellipsoid and more sharply marginated. The degeneration is as a rule more intense in granuloma annulare.

3. The diffuse arrangement of the infiltrate in the lesions of necrobiosis lipoidica diabeticorum stands in contrast to the radial or palisade arrangement in lesions of granuloma annulare.

4. The infiltrate in both diseases is made up of varying proportions of fibroblasts, lymphocytes, histiocytes and epithelioid cells. In necrobiosis, especially, fibroblasts may be so prominent that the picture simulates that of subepidermal fibrosis. In other cases there may be so many epithelioid cells (and giant cells, which are more frequent than in granuloma annulare) that the structure is frankly tuberculoid and, especially, may simulate the histologic picture of sarcoid.

5. Intimal proliferation and obliterative changes in the blood vessels are much more frequent and prominent in necrobiosis.

6. Deposits of lipids are almost always present in necrobiosis; they may be present in granuloma annulare.

7. With the use of various methods of staining, the two diseases can usually be differentiated histologically.

ABSTRACT OF DISCUSSION

DR. MARCUS R. CARO, Chicago: Dr. Laymon and his collaborator are to be congratulated on a thorough histologic study of a large group of cases of this hitherto rare disorder. Their paper is an important contribution to the understanding of a dermatosis which, in spite of its infrequency, has from its earliest recognition been a source of great controversy.

The controversial issue at first was its name, with "dermatitis atrophicans lipoides diabetica" losing ground from the start. More recently, the struggle has been for recognition of its very existence as an entity, distinct from granuloma annulare. The problem of nomenclature should finally be settled on a rational basis.

The two features constantly present in the lesions of this disease are necrobiosis and lipids. Diabetes mellitus, while present in most cases, is absent in a sufficiently large number to provoke discussion of this feature whenever a case is presented before any dermatologic society. It think that the descriptive term "diabeticorum" should be dropped, as suggested by Ellis and Kirby-Smith,[9] and that the disease should be known simply as necrobiosis lipoidica.

As to its identity as a separate disease, I subscribe fully to the views of the authors that necrobiosis lipoidica has nothing in common with granuloma annulare except a rare resemblance in the gross appearance of the lesions and an occasional one in the histologic features.

When a case of either disease is studied throughly, the combination of clinical features, and generally the histologic picture, may be depended on to differentiate the two conditions clearly. It must be remembered in the histologic study of cutaneous lesions, that all diseases are manifested by pathologic changes in the relatively few elements of which the skin is composed. Because the possible

changes in these elements are comparatively few and limited, it necessarily follows that in many different diseases the stimuli present will produce changes which may be similar, or at times identical. Dr. Beerman showed us that similar histologic features may be present in the lesions of keratosis follicularis and in those of nevus syringoadenomatosus papilliferus. Dr. Laymon has reminded us that the lesions of syphilis and tuberculosis may at times resemble each other histologically. Likewise, the sarcoid reaction in the skin may be produced by such different diseases as tuberculosis, leprosy and syphilis or by the presence of a foreign body. In spite of such histologic similarity, all these diseases are accepted as being unrelated to each other etiologically or in any other manner.

I feel certain that when the exact etiologic factors are finally determined for necrobiosis lipoidica and granuloma annulare and their pathogenesis is fully understood the occasional histologic resemblance of these diseases will be considered unimportant.

Dr. Francis A. Ellis, Baltimore: Dr. Laymon and Dr. Fisher have reported and compared an unusually large series of cases of necrobiosis lipoidica and granuloma annulare.

I agree with Dr. Caro that it may be opportune to drop the word "diabeticorum," as I have seen a high percentage of cases in nondiabetic persons—to be exact, 6 in 10 cases. Dr. Pepple reported that he has had 4 cases in the last two years and that all the patients were nondiabetic. Of the cases reported in the literature since 1942, 35 per cent were of nondiabetic persons. One patient whose case was reported in 1941 (F. A. Ellis: Necrobiosis Lipoidica: A Form of Granuloma Annulare? Arch. Dermat. & Syph. **43**:822-828 [May] 1941) has been followed for fifteen years and is still nondiabetic at the time of writing.

Following Dr. Montgomery's lead, I have tried to demonstrate mucinous degenerations but have found only a fair amount in the sclerotic area in a biopsy specimen from a nondiabetic patient with necrobiosis lipoidica. The appearance of the lipid droplets in chains and clusters may suggest imbibition rather than degeneration. The fat globules tend to be deposited where the early degenerative alterations are occurring and may disappear in the center of the older sclerotic areas.

Dr. Laymon did not discuss what these lesions were called before publication of the reports of Oppenheim and Urbach. Necrobiosis lipoidica is certainly not a new disease, and Dr. Traub and others (cited by Ellis and Kirby-Smith [9]) have suggested that it is simply a new name for such diseases as localized scleroderma (morphea) with a tuberculoid architecture.

The pathologic changes in granuloma annulare are less advanced and more superficial than those in necrobiosis lipoidica, and in the latter they may mimic erythema induratum. Both the diseases under consideration are characterized by well defined perivascular areas of infiltrate composed of small mononuclear leukocytes and situated just beyond the periphery of the necrobiotic areas, and just beyond these zones of infiltrate may be seen tuberculoid architecture, especially in necrobiosis lipoidica.

One third of our early series showed some ulceration, and other reports of cases with ulceration have been presented. Dr. Burgess, at the present meeting, reported a case with ulceration. It is my impression that ulceration is not so rare as Dr. Laymon suggests. One of my cases of granuloma annulare showed ulceration, but this feature may have been factitial.

Dr. Laymon describes the necrosis he saw in cases of granuloma annulare. I did not see true necrosis. Possibly it would be better, in the present state of

knowledge, to adhere to the term "necrobiosis" rather than to "necrosis." It is my impression that there is a more advanced necrobiosis in necrobiosis lipoidica and that this and a tendency to a tuberculoid architecture at the periphery of the necrobiotic areas are the most striking features differentiating necrobiosis lipoidica from granuloma annulare.

Few sections have been examined which were taken from patients in early stages of necrobiosis lipoidica, in which the lesions are small. Investigators have seldom compared the early stages with granuloma annulare. Palisading is apparently less in necrobiosis lipoidica, but perhaps this feature has been missed because we have seen the late stages and because the process has extended and involved the peripheral area, thus effacing this particular feature.

I consider the vascular changes to be, not primary, but secondary. If they are to be considered primary, the tissues in question will certainly have to be compared with a number of normal tissues and with tissues from corresponding locations in patients with similar general physical conditions and of the same age.

In tuberculous lesions occurring on the legs the alterations are more advanced than in those on the upper extremities. This factor should be taken into consideration when we compare the two diseases. Dr. Laymon did not stress sufficiently the fact that difference in location of the lesions may be an important factor. For example, the clinical and histologic pictures of papulonecrotic tuberculoid lesions on the face and upper extremities differ from those on the lower extremities. Even such a simple disease as impetigo or ecthyma may show different clinical and histologic features when the lesions appear on the lower extremities from those present when they occur on the upper extremities.

Dr. Louis H. Winer, Beverly Hills, Calif.: Histologically, necrobiosis has always seemed to me a more diffuse process than granuloma annulare.

Necrobiosis frequently reminds one of subepidermal fibrosis, but the bluish discoloration of the cells when they are stained with hematoxylin and eosin indicates that one is not dealing with that disease. Granuloma annulare in a section stained with this method is characterized by necrosis in the centrally located tissues, in which the cells lose their nuclei, and some become lipid and are surrounded by a palisade arrangement. This typical arrangement may be quite variable, so that one may see multiple atypical foci.

That there is a difference in the types of degeneration of collagen is evident from the sections stained with hematoxylin and eosin in these two conditions: in necrobiosis the altered collagen takes on a faint bluish stain, whereas in granuloma annulare it is a lighter pink.

The lipids in the lesions of necrobiosis lipoidica diabeticorum are equally distributed. Each cell is undergoing the change, and there is a smoothness to the picture, sometimes even to the point of simulating the evenness of xanthoma. In the lesions of granuloma annulare, on the other hand, although the fats may be diffuse, there is lumpiness, consisting of a mass here and there.

I have seen histopathologic sections of sarcoids that also had these diffuse globules of fats, not evenly spread out, but in irregular, massive, lumpy arrangement.

Specimens for biopsy should be taken with caution in cases of the necrobiosis, for an occasional ulcer thus produced fails to heal. The removal of a specimen for biopsy does not stimulate healing in necrobiosis. It has been reported to stimulate healing in granuloma annulare, but I have not often found that to be true.

Dr. Carl W. Laymon, Minneapolis: Dr. Ellis brought out that necrobiosis undoubtedly existed long before it was described by Oppenheim and Urbach. In all probability, a variety of different terms were applied to it, such as atypical xanthoma diabeticorum, morphea and granuloma annulare.

In the presentation, there was insufficient time to comment on the pathogenesis. Oppenheim stated the opinion that there was actual lipid degeneration of the collagenous tissues. Urbach, on the other hand, stated the belief that certain toxic substances present in patients with diabetes led to necrobiosis, followed by imbibition of lipids. This, of course, does not explain the occurrence of necrobiosis in nondiabetic patients. Gottron and Boldt noted that certain persons have vasomotor stigmas, as manifested by a tendency to flushing, hyperhidrosis, claudication, hypertension and changes in the cutaneous vessels, which lead to necrobiosis. Thannhauser stated the belief that toxic substances play no role in the pathogenesis of necrobiosis.

Dr. Fisher and I feel that necrobiosis and granuloma annulare are separate entities, rather than variants of the same disease. Undoubtedly, however, there are instances in which both the clinical and the histologic features of the two diseases are almost identical. This is true in other diseases, for example, lupus vulgaris and late syphilis. In arriving at a decision, however, one must use data from the majority of cases rather than from the occasional exception. Certainly, in most cases of necrobiosis it is possible to make a differentiation from granuloma annulare if one studies the cases carefully clinically and histologically.

LARGE SPORES (MACROCONIDIA, FUSEAUX) OF MICROSPORUM CANIS IN VIVO

Report of Two Cases

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LYNN, MASS.
AND
HARVEY B. ANSELL, M.D.
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DOES Microsporum canis ever produce macroconidia (fuseaux) during its parasitic life cycle in tinea capitis (ringworm of the scalp)?

We have not found any mention of this possibility in the literature. Gregory [1] stated: "While parasitic in the skin [?] the dermatophyte thallus is differentiated only into hyphae and small round thallospores or oidia." Davidson and Gregory [2] stated unequivocally: "So long as hairs infected with microsporon audouini, trichophyton gypseum, and other ringworm fungi remain attached to the body, the fungi attacking them consist only of hyphae and small round spores."

A review of other literature and texts on dermatology and mycology failed to reveal any mention of the possibility of production of macroconidia during the parasitic phase of infection with ringworm fungi. In addition to other sources, texts by the following authors were consulted: Lewis and Hopper, Dodge, Swartz, Conant and others, Langeron, Morris, Becker and Obermayer, Ormsby and Montgomery, Tobias, Andrews, Savill, Stelwagon and Gaskill, Lewis and Hopper, Pusey, Darier, Highman and Jackson.[3]

From the Department of Dermatology and Syphilology, Boston City Hospital and Tufts College Medical School; Dr. J. G. Downing, Chief.

1. Gregory, P. H.: The Dermatophytes, Biol. Rev. Cambridge Philos. Soc. **10**:216, 1935.

2. Davidson, A. M., and Gregory, P. H.: Development of Fuseaux, Aleuriospores and Spirales, Nature, London **131**:836, 1933.

3. Lewis, G. M., and Hopper, M. E.: An Introduction to Medical Mycology, ed. 2, Chicago, The Year Book Publishers, Inc., 1943. Dodge, C. W.: Medical Mycology, St. Louis, C. V. Mosby Company, 1935. Swartz, J. H.: Elements of Medical Mycology, New York, Grune & Stratton, Inc., 1943. Conant, N. F., and others: Manual of Clinical Mycology (Military Medical Manual, National Research Council), Philadelphia, W. B. Saunders Company, 1944. Langeron, M.: Précis de mycologie, Paris, Masson & Cie, 1945. Morris, M.: Ringworm in the Light of Recent Research, London, Cassell & Co., Ltd., 1899. Becker, S. W., and Obermayer, M. E.: Modern Dermatology and Syphilology, ed. 2, Philadelphia,

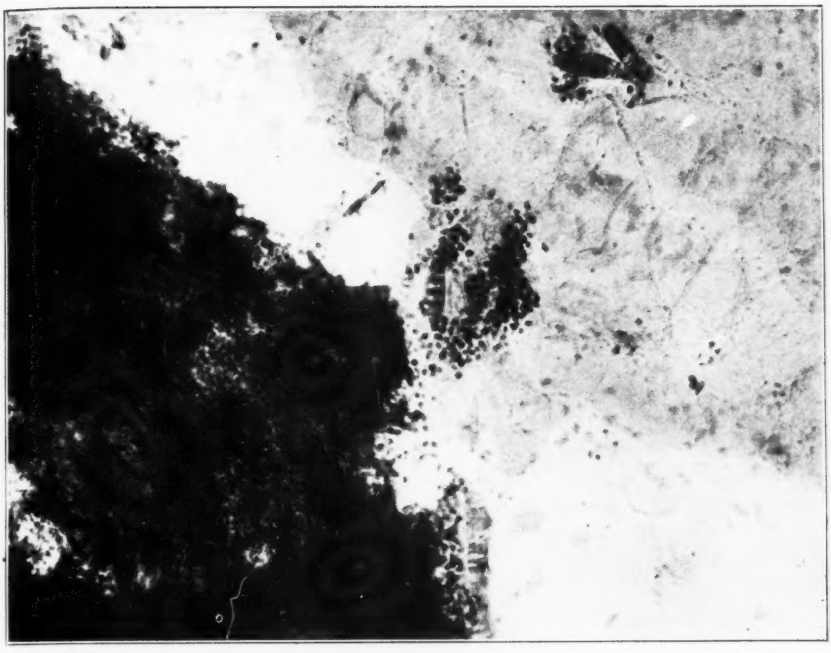

Fig. 1.—From notes of the late Dr. Ernst Bernhardt: "Fuseaux may be found on a typical hair infected with M. Canis immediately after its epilation; these may have well defined compartments, as in the spindle in the center of the photomicrograph, or be somewhat deformed, like those above and below it." × 310.

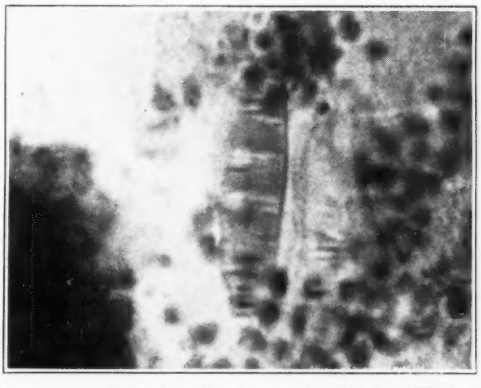

Fig. 2.—From notes of the late Dr. Ernst Bernhardt: "Higher magnification (× 850) of the fuseau in the center of figure 1. Dr. J. G. Downing considered this type of spindle a fuseau years before a newer staining technic rendered its identity obvious, as shown here. Formerly, it was confused with the spindle cells from normal scalps, seen in preparations containing potassium hydroxide and considered epithelial cells by Sabouraud (Maladies du cuir chevelu: III. Les maladies cryptogamiques; les teignes, Paris, Masson & Cie, 1910)."

The typical large, boat-shaped macroconidia, called fuseaux, are routinely observed in cultures on artificial mediums. They have also been noted by Davidson and Gregory [4] in cultures in situ, that is, in infected hairs removed from a patient and suspended in van Tieghem cells containing solutions of known osmotic pressure in the bottom. The hairs and the fungus within them were supplied merely with water vapor. (The hairs had remained dry between sterilized glass slides for about six months prior to the experiment.)

The ultimate significance of the two forms of spores in the life cycle of the fungus is not clearly known. It is obvious, however, that environment determines the development of the type of spore. The explanation by Gregory,[1] that an increase in the supply of water vapor alone is adequate to encourage the formation of macroconidia, seems too simple. It is possible that the development of macroconidia is suppressed in vivo because of the lack of some substance, but it is more probable that there is present on the normal human scalp some substance which inhibits the formation of macroconidia. When freed from the presence of this theoretic inhibitor, i.e., in the van Tieghem cell, the fungus can produce its spiral mycelium and macroconidia, elements which characterize its saprophytic phase. This is, however, speculation.

In 1936, routine examination of a patient with tinea capitis at the Boston City Hospital disclosed in direct examination of an epilated hair objects identified by Dr. John G. Downing as fuseaux. They were also seen by one of us (B. A.). The episode caused a minor flurry of excitement, but, unfortunately, the details of the case were lost. Some years later, the late Dr. Ernst Bernhardt, mycologist to the department of dermatology and syphilology at Boston City Hospital, came across a similar case. He was preparing material for a

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J. B. Lippincott Company, 1947. Ormsby, O. S., and Montgomery, H.: Diseases of the Skin, Philadelphia, Lea & Febiger, 1943. Tobias, N.: Essentials of Dermatology, ed. 2, Philadelphia, J. B. Lippincott Company, 1944. Andrews, G. C.: Diseases of the Skin, ed. 3, Philadelphia, W. B. Saunders Company, 1946. Savill, A.: The Hair and Scalp, Baltimore, Williams & Wilkins Company, 1945. Stelwagon, H. W., and Gaskill, A.: Diseases of the Skin, ed. 9, Philadelphia, W. B. Saunders Company, 1921. Lewis, G. M., and Hopper, M. E.: Fungi, in Sutton, R. L., and Sutton, R. L., Jr.: Diseases of the Skin, St. Louis, C. V. Mosby Company, 1939. Pusey, W. A.: The Principles and Practice of Dermatology, New York, D. Appleton & Company, 1907. Darier, J., in Pollitzer, G.: Text Book of Dermatology, Philadelphia, Lea & Febiger, 1920. Highman, W. J.: Dermatology, New York, The Macmillan Company, 1921. Jackson, G. T.: Diseases of the Hair and Scalp, New York, E. B. Treat, 1898.

4. Gregory.[1] Davidson, A. M., and Gregory, P. H.: In Situ Cultures of Dermatophytes, Canad. J. Research **10**:373, 1934.

communication on it when he died; figures 1 and 2 and their legends were, regrettably, the only material on the case discovered after his death.

REPORT OF CASES

CASE 1.—G. M. H., a 16 month old girl, was examined on March 7, 1947 (fig. 3). The mother stated that the child's scalp had become dry two months previously; there had been no itching, but crusting had soon developed. Treatment was prescribed for this condition at an outpatient department. For about two weeks

Fig. 3.—Sixteen month old girl with an area of partial alopecia over the right parietal area, from which was removed the hair illustrated in figures 4 and 5.

the condition seemed to improve, but the treatment then proved ineffective. An older brother had had "ringworm of the face" two months before, after playing with a kitten.

The patient had an area of alopecia, about 4 cm. in diameter, over the right parietal region of the scalp; in it, very short stubs of hair could be seen on close inspection. Under illumination through Wood's filter typically brilliant fluorescent hairs were seen, not only in the area of alopecia, but scattered over the right side of the scalp.

Some of the fluorescent hairs were plucked and planted on Sabouraud's dextrose agar and several were examined in lactophenol-cotton blue (anilin blue) stain.

To our amazement, several hair stubs were filled not only with a mass of small, round spores but with large, boat-shaped fuseaux, which took the cotton blue stain deeply. However, the fuseaux lost their sharpness and distinction before photomicrographs were made (fig. 4). Some of the cotton blue had diffused out of the cells, softening the outlines. Cultures on Sabouraud's agar and on rice were characteristic of M. canis in every respect.

The patient was seen weekly for five weeks. During this time and thereafter, although many fluorescent hairs were examined, no more fuseaux were seen; only typical masses of small, round spores were noted. On May 29, almost three months later, another somewhat uncommon phenomenon was observed in one of the hairs

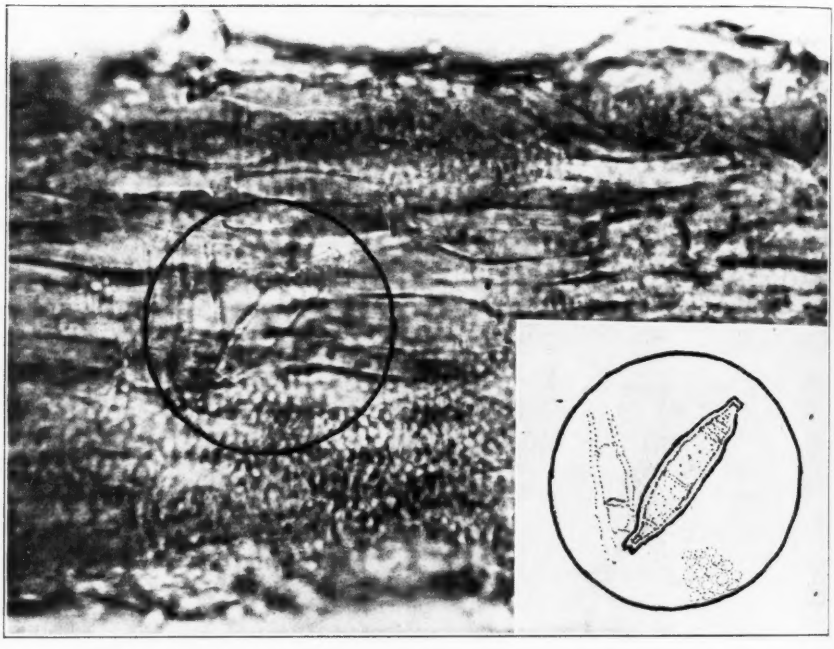

Fig. 4.—Fuseau in fairly sharp focus throughout its entire length, showing the thick, double-contoured wall, the tapering, blunt ends and the septations.

epilated from the patient's scalp: Long chains of arthrospores, branching dichotomously in the direction of the hair bulb, were present in the shaft of the hair (fig. 5).

Treatment up to this time had been of the classic conservative type, consisting of frequent shaving of the entire scalp and application of a succession of mixtures of commonly used fungicides. At the time of writing a polysulfide ointment has been added, but the infection is still present.

Case 2.—On July 19, 1947, L. A. V., a 3½ year old girl, was seen. The mother had first noticed a bald area on the child's scalp three days before. She had recently been playing with some kittens whose conditions and whereabouts could not subsequently be determined. A large area of alopecia, about 4 cm. in diameter, was present over the left parietal area of the scalp, and a small, round lesion was on the

dorsum of the left wrist. Both these areas showed typical brilliant fluorescence under Wood's filter. Hairs from the scalp and wrist were epilated, placed between two clean glass slides and wrapped in clean paper. Three days later, some were planted on Sabouraud's dextrose agar and some examined directly. Microscopic examination of the lanugo hairs epilated from the lesion on the wrist showed infection with small, round spores. During examination of one of the hairs from the scalp, a single large, typical septate, tapered, boat-shaped fuseau was observed lying next to it. A search revealed several hairs filled with fuseaux and with chains of arthrospores.

Fig. 5.—Hair in lactophenol–cotton blue stain, showing dichotomously branching chains of arthrospores. From one of the arthospores a hypha is growing directly out through the cuticle of the hair shaft. The deep color of the cytoplasm stained with cotton blue contrasts with the clear hyalin of the cellular walls.

The morphologic features of many of these fuseaux did not permit of immediate identification. Some did not show clearly the double contour of the wall. Most of them were recognizable only by their outline; the septations and the morphologic character of their cytoplasm were not distinguishable. Whether this state was due to a degenerative change after the fuseaux were once clearly formed or whether these fuseaux were in an aborted phase is a matter of speculation.

A hair epilated from the patient at the same time was later attached to the under surface of the cover slip of a van Tieghem cell with only a tiny speck of Sabouraud's dextrose agar. After about five days, it grew a typical mass of

aerial hyphae with terminal fuseaux (a repetition of the culture in situ of Gregory and Davidson [4]).

The patient was treated with the usual conservative methods: application of ointment containing salicylic acid and sulfur, of ointment containing iodine and, for two weeks after August 23, of antiscabious polysulfide ointment. After September 6 no medication at all was ordered, and the patient was again examined on September 13. There were then several small, more scattered areas of fluorescence in addition to the original large area. A number of hairs from these areas, examined immediately after epilation, were heavily infected with fuseaux! One hair shaft appeared packed with fuseaux which had rapidly and avidly taken the analine blue stain. In the same hair, however, many fuseaux did not stain at all.

After preparation with a solution containing 40 per cent sodium hydroxide and 10 per cent glycerin, one hair showed fuseaux so faintly outlined that if one had not been consciously looking for them they would undoubtedly have been missed, especially because the spawnlike mass of small, round spores could easily have distracted the observer's attention.

Cultures on Sabouraud's agar and on rice grew typical M. canis.

CONCLUSIONS

The large spores (macroconidia, fuseaux) of M. canis can be produced in vivo, in the hair of infected children.

Two cases from private practice and 1 case from the records of the late Dr. Ernst Bernhardt in which fuseaux were found in epilated hairs are reported.

The rarity of this phenomenon is stimulating to speculation on its significance. The correct explanation will probably shed more light on the relation of infection to spontaneous cure after puberty.

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HUMAN INFESTATION WITH SCABIES OF MONKEYS

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AND
MILTON D. FELDMAN, M.D.
CINCINNATI

MANY kinds of animals and birds are infested with itch mites of different types. Each species of the mite is for the most part restricted to a habitual host. However, sometimes human beings, as a consequence of close contact with infested animals, acquire the infestation. This is true for dog and cat and uncommonly for avian infestations. Little is known about scabies in the monkey. A case of infection with Sarcoptes scabiei from an orangutan was presented by Weidman [1] in which a single female acarus and several ova were found on scrapings. These were identical with the form seen in human beings. Toomey,[2] in his extensive paper on scabies of animal origin, referred to Weidman's case and stated that several animals, among which is the monkey, rarely cause scabies in human beings. Scabies from animals, then, is uncommon among attendants at Zoological Gardens. Mellanby,[3] in his vast experience with scabies, has never observed spread from monkey infestation.

We wish to report an outbreak of scabies in a group of 10 gibbons, two genera (Hylobates and Symphalangus) of apes of Asia and the East Indies. The gibbons were shipped to the United States from Siam. On arrival at the Zoological Gardens, nothing remarkable was noted except that the animals scratched. As many monkeys scratch, no special attention was paid to this. On removal to winter quarters, the animals were observed to have increased weakness, scaling of the skin, loss of weight and tremors. Nine died. Postmortem examinations were performed by Dr. Pearl Zeek [2] and Dr. Richard Wilson [3] of the department of pathology on 3 animals; they reported no gross visceral changes except a hamartomatous tumor of the spleen in 1 animal.

From the Department of Dermatology and Syphilology of the College of Medicine of the University of Cincinnati.

1. Weidman, F.: Case Presentation, Arch. Dermat. & Syph. **5**:675 (May) 1922.

2. Toomey, N.: Scabies of Animal Origin, Urol. & Cutan. Rev. **26**:473 (Aug.) 1922.

Detailed dermatologic examinations were done on 3 gibbons. The skin of the entire extremities and of the lower trunk was diffusely infiltrated, scaling and denuded of hair. These changes and the histologic observations reminded one of the rare scabies norvegica of human beings. Sarcoptes were easily isolated from the skin of the gibbons and appeared similar to the sarcoptes of infestations in human beings. Like scabies norvegica, excessive numbers of parasites were found. E. W. Baker, of the Bureau of Entomology, United States Department of Agriculture,[3] reported the specimen to be Sarc. scabiei (Degeer) and stated that it "represented one of the unnamed varieties which has been discussed on the basis of host relations rather than

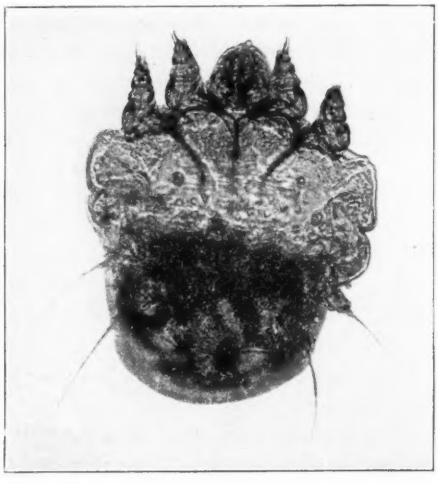

Fig. 1.—Photomicrograph of an acarus obtained from an interdigital area of a gibbon. (Permount mounting.)

morphologic distinctions." Culture of hair and scales revealed aspergilli. Microscopic examination of the skin of the gibbons revealed decided hyperkeratosis, parakeratosis, crusting and the presence of many parasites, burrows and ova within the epidermis. There was also extensive tunneling into the hyperkeratotic zones. There was only a moderate degree of perivascular inflammatory reaction in the cutis. In general, the picture resembled that described in scabies norvegica except that burrows appeared more superficial.

The systemic background in the gibbons, on which this severe scabies developed, was considered. Scabies norvegica has usually been found to be associated with malnutrition, wasting diseases, chronic infections, psychoses and poor hygiene. It was believed that the

following factors were important: removal of the animals in winter quarters and out of the sunlight, the restriction of their activities in winter quarters and the probable inadequate maintenance of a good nutritional state, together with possible viral infections.

Fig. 2.—Photograph of the arm of one gibbon showing similarity to scabies norvegica of human beings.

Five helpers and the superintendent of the Zoological Gardens, complained of pruritus and eruption. The wives and 3 children, who had been in intimate contact while caring for these animals, of 2 of them had similar complaints. One member of the resident staff of the department of dermatology and syphilology, who had handled postmortem cutaneous material of the gibbons and who had

treated several of the attendants, became infested. The dermatitis present in all of these persons was characteristic of the typical scabetic infestation as seen in human beings with predilection for the interdigital areas, axillary folds, penis and buttocks. Postscabietic nodules of the scrotum developed in 1 person. The eruption spared the face in all instances. The acarus was obtained from interdigital lesions in 1 attendant and in the resident physician. These were similar to the acari obtained from the gibbons.

Treatment of the condition in the human subjects with rapid cure was accomplished either with benzyl benzoate and dichlorodiphenyl-trichloroethane (gratavec® ointment) mixtures or 1 per cent of the gamma isomer of 1, 2, 3, 4, 5, 6-hexachlorocyclohexane in a vanishing cream base (kwell® ointment). These mixtures and also chlordane were considered as treatment agents for the animals. However, their poor condition and the possibility of toxic effects from oral ingestion precluded the use of such strong medicaments, so that a sulfur dip was attempted first. One animal died in the bath and 1 shortly afterward.

CONCLUSIONS

Scabies involved a group of 10 gibbons sent from Siam. Five persons who cared for these animals contracted the disease. Scrapings from the animals' tissue revealed many parasites identical with the Sarcoptes organism of infestations in human beings. The clinical and histologic picture in the gibbons suggested a scabies norvegica type. All of the gibbons eventually died. The clinical picture in the human subjects was that of a typical and mild scabies infestation.

KERATOSIS (SEBORRHEIC AND SENILE)

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GEORGE M. MacKEE, M.D.
AND
PERRY M. SACHS, M.D.
NEW YORK

IN THE past, the keratoses arising in senile or actinic skin were considered in the same category and not differentiated. The nomenclature and descriptions of these lesions caused confusion. More recent investigation has recognized two types,[1] the senile (senile keratosis, keratoma senilis, hyperkeratosis senilis) and the seborrheic (seborrheic keratosis, verruca senilis, verruca seborrheica). With minor variation, this view has been accepted, and, while it does include the chief characteristics, some misunderstanding still remains, particularly as to the nomenclature.

We feel that a further subdivision may be useful in formulating a clearer, more concise and more universal concept of the subject. Our studies and observations, over a period of many years, led us to conclude that there are four principal lesions, each with a distinct clinical and microscopic picture; the senile and seborrheic keratoses and the senile and seborrheic verrucae. The latter ones, respectively, develop from the former and represent a more advanced stage. The different types of malignant change and the variation in frequency of such change noted in each member of the group further emphasize the importance of this classification.

Seborrheic keratosis and seborrheic verruca are of much more frequent occurrence than senile keratosis and senile verruca. As a rule, malignant change in the senile type is of more serious significance and of greater incidence than in the seborrheic type. There is considerable difference of opinion as to whether or not the lesions of the seborrheic type ever give rise to cancer. Hartzell,[2] Dubreuilh,[3] McCarthy,[4] Eller

From the Skin and Cancer Unit, New York Post-Graduate Medical School and Hospital.

1. MacKee, G. M., and Cipollaro, A. C.: Cutaneous Cancer and Precancer, New York, American Journal of Cancer, 1937.

2. Hartzell, M. B.: Some Precancerous Affections of the Skin, More Particularly Precancerous Keratoses, J. Cutan. Dis. **21**:393-403, 1903.

3. Dubreuilh, W.: Des hyperkeratoses circonscrites, Ann. de dermat. et syph. **7**:1158-1204, 1896.

4. McCarthy, C. L.: Histopathology of Skin Diseases, St. Louis, C. V. Mosby Company, 1931.

and Ryan [5] and others, including us, have stated the belief that they have seen epitheliomas, usually of the basal cell type, develop in these lesions. On the other hand, such excellent dermatologists as Jadassohn,[6] Bloch,[7] Freudenthal [8] and Hookey [9] have never seen anything suggestive of malignant change in this type.

SEBORRHEIC KERATOSIS

The lesion of seborrheic keratosis evolves slowly and usually is approximately 0.5 to 1 cm. in diameter. It is sharply circumscribed,

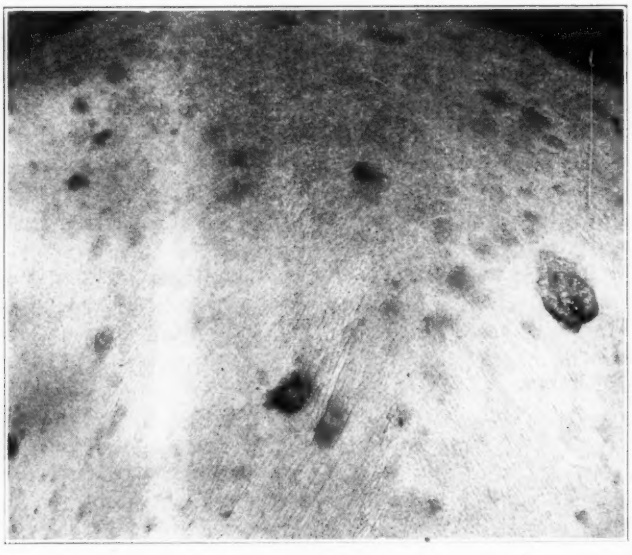

Fig. 1.—There are numerous small flat seborrheic keratoses on the back. Several large raised verrucous seborrheic verrucae are present.

round or oval, superficial and nonindurated and may be slightly elevated. The surface may be smooth, rough or slightly verrucous and is often

5. Eller, J. J., and Ryan, V. J.: Senile Keratoses and Seborrheic Keratoses: Differences Clinically, Histologically and in Susceptibility to Malignant Change, Arch. Dermat. & Syph. **22**:1043-1060 (Dec.) 1930.

6. Jadassohn, J., cited by McCarthy.[4]

7. Bloch, B.: Cancers and Precancerous Affections from the Dermatological Viewpoint, Cancer Rev. **7**:65-98, 1932.

8. Freudenthal, W.: Rumpfhautepitheliom (nebst Bemerkungen uber die Verruca senilis und das Keratoma senile), Arch. f. Dermat. u. Syph. **158**:538-544. 1929.

9. Hookey, J. A.: Keratoma Senilis and Verruca Senilis, Arch. Dermat. & Syph. **23**:946-959 (May) 1931.

covered with a loose steatoid horny layer which is easily removed without bleeding. The color varies from yellow to deep brown. The yellow often gives the appearance of a superficial xanthoma. Keratoses of this type occur chiefly on the trunk and on the face (figs. 1 and 2). They are commonest in elderly persons but are seen occasionally in younger persons. The lesions may be single, few or many.

Histopathologically, the epidermis is thin, not acanthotic, and regularly extends upward as fairly uniform digitations resulting in the verrucous surface. The horny layer is thickened and loosely arranged

Fig. 2.—Many flat slightly elevated small seborrheic keratoses are seen on the face and forehead.

and may dip into the lumen of the follicles. The granular layer is present but not increased. The basal cell margin is not disturbed, and the epidermal cells show no abnormal changes.

The papillary bodies are elongated, corresponding to the upward projections of the epidermis. There is little or no inflammatory reaction, and the picture may simulate a nevus or verruca plana juvenilis. It is not uncommon to find basophilic degeneration in the upper part of the cutis (fig. 3). While the microscopic picture is fairly characteristic, usually it is not seen as a pure seborrheic keratosis but more often as the transition into the early stage of seborrheic verruca (fig. 4).

Malignant change is an infrequent observation in a seborrheic keratosis. In our experience, when it occurs, basal cell epithelioma is the neoplasm most commonly seen. On rare occasions, we have observed anaplastic epithelioma. We have not seen prickle cell epithelioma associated with seborrheic keratosis.

SEBORRHEIC VERRUCA

Seborrheic verruca is a further stage of development of seborrheic keratosis and most probably is its only means of evolution. Clinically, seborrheic verrucae are of frequent ocurrence. They may be single or fairly numerous, and associated keratoses need not be present. Where many seborrheic keratoses are found, as on the trunk, one or only a few of the lesions may manifest the alteration into seborrheic verrucae.

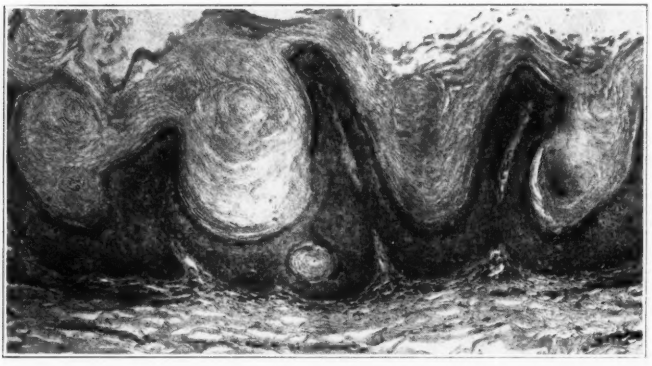

Fig. 3.—The following microscopic observations of a seborrheic keratosis are noted: thin epidermis, upward projections of the epidermis, a loosely laminated horny layer and a mild inflammatory reaction (× 70.3).

When the keratosis becomes a verruca, the lesion increases in size and becomes raised and the surface is more verrucous. Slight or moderate induration can be felt. The color is deep brown or almost black. In both the seborrheic keratosis and the seborrheic verruca, often it is posible to detect patulous plugged follicular orifices. The clinical picture strongly suggests a nevus of the intraepidermic type. The microscopic observations, likewise, show a close resemblance. Because of the similarity, the seborrheic verruca sometimes is referred to as the nevoid verruca or nevoid keratosis (figs. 1 and 5).

The microscopic picture reveals that the epidermis of the seborrheic keratosis becomes acanthotic and arranged in anastomosing bands. Within this coarse epithelial network are islands of connective tissue and horn cysts representing sections of papillae and hyperkeratotic

Fig. 4.—The transition of seborrheic keratosis into seborrheic verruca is shown. Early anastomosing bands of epidermis, containing horn cysts and papillary bodies, are noted (× 77.8).

Fig. 5.—There is a large seborrheic verruca (nevoid) on the temple. Several seborrheic keratoses are seen.

follicles, as well as the tops of the verrucous surface, cut at various levels. The surface is distinctly verrucous, the palisade basal layer is unaltered and may contain considerable pigment. In the early stage of the process, the horny layer is loose and separated and the granular layer is not increased. Later, the horny layer becomes more compact and the underlying granular layer more pronounced.

At first, there is a mild subepidermic inflammatory reaction; later this is more intense, and, in addition to small round cells, plasma cells may be noted in the infiltration. A variable amount of basophilic degeneration is seen (fig. 6).

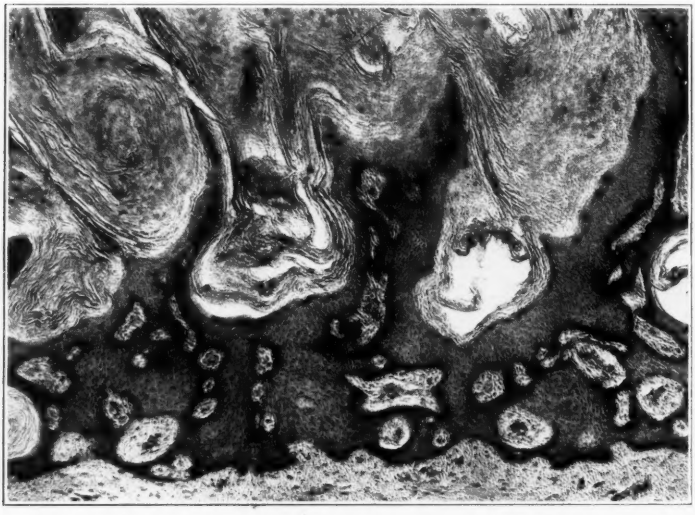

Fig. 6.—This shows a fully developed seborrheic verruca. There is an increased horny layer and an acanthotic epidermis arranged in a coarse network (× 66.4).

Malignant neoplasms originating in seborrheic verrucae, though uncommon, are more frequent than in seborrheic keratoses. Most types of epithelioma, including basal cell, mixed cell, prickle cell and anaplastic cell, can arise from a seborrheic verruca; the first two are the usual ones, while the others seldom are seen.

Basal cell epithelioma may develop within the lesion and be of the pure form or can be associated with Bowen type change. On occasions, they may spring and infiltrate from the lower border of the epidermis.

Mixed cell epithelioma is not a particularly good name but does express the general idea of the growth. We are not completely acquainted

with the full significance of this neoplasm. It is composed of basal and prickle cells arranged in segregated masses; yet, it differs from spinobasal cell epithelioma (intermediary, transitional cell or baso-squamous cell epithelioma). The latter is a basal cell epithelioma, with an occasional whorl, pearl or some cells closely resembling prickle cells. In short, spinobasal cell epithelioma is a basal cell

Differentiated Characteristics

	Seborrheic Verruca with Mixed Cell Epithelioma	Intraepidermic Epithelial Nevus
Horny layer	May be entirely or in part loosely arranged	Densely packed
Epitheliomatous elements	Not uniformly arranged	Alternate regularly
Pigment	Infrequent	Frequent
Basophilic degeneration	Often	Seldom
Inflammatory zone	Always present	Absent unless secondarily traumatized

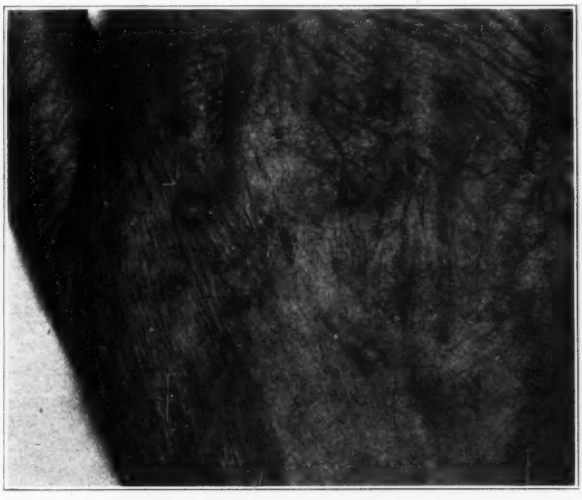

Fig. 7.—Several senile keratoses of the papillose type are present on the dorsum of the hand.

epithelioma with an attempt at prickle cell epithelioma formation, while the mixed cell type is composed of distinct masses of basal cell epithelioma and prickle cell epithelioma, as one neoplasm.

It is not easy nor always possible to differentiate the microscopic picture of seborrheic verruca with mixed cell epithelioma from the intraepidermic epithelial nevus. The data in the table may be useful.

SENILE KERATOSIS

We believe that there are two varieties of senile keratoses: the papillose and the flat. The clinical appearance, the location and the microscopic pictures differentiate these.

The papillose type of senile keratosis is seen most commonly on the face and dorsa of the hands and forearms—in other words, in the areas that are exposed most frequently to direct or indirect solar radiation. Occasionally, it occurs on the trunk or other parts, even

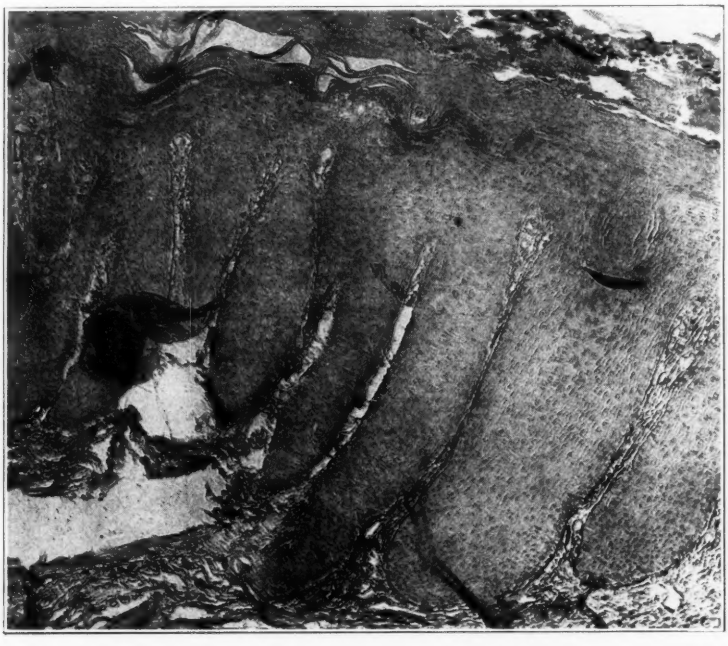

Fig. 8.—The features of the papillose type of senile keratosis are seen. The rete pegs are acanthotic, the surface is covered with a densely laminated hyperkeratosis and a moderate cellular reaction is present in the subepidermic region (× 87.5).

when such regions have not been exposed to sunlight. It affects chiefly elderly persons, although it is sometimes encountered in the third and fourth decades. It is rarely observed in Negroes, American Indians or Arabs. The lesions range in diameter from 1 or 2 mm. to 1 cm. or more. They develop, as a rule, in the skin that shows either macroscopic or microscopic evidence of actinic sequelae. They are often multiple, but less numerous than seborrheic keratoses. The lesions are well defined, indurated, deep gray to almost black and

covered with dense, usually adherent, hyperkeratosis. The surface is verrucous and cannot be removed without bleeding. Popular concept and the literature lead to the belief that this is a common dermatosis, but we have been impressed by its infrequency. Possibly, these lesions are more evident in rural districts than in large cities (fig. 7).

Histologically, the epidermis is acanthotic and has large elongated rete pegs. The granular layer is present and often increased. The surface is verrucous and covered with an increased densely laminated horny layer. The basal cell margin is unaltered. No other abnormal changes are noted in the epidermis.

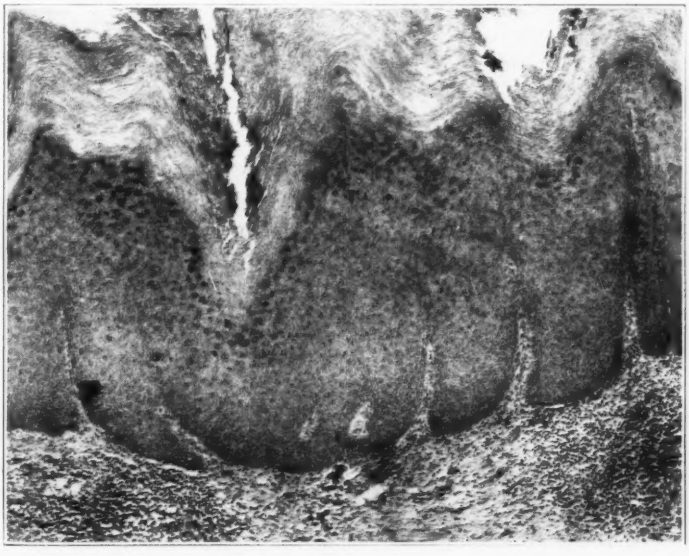

Fig. 9.—This demonstrates the microscopic features of the papillose type of senile keratosis with beginning senile verruca. In one area an early senile acanthoma can be seen (× 63).

A mild inflammatory process can be seen in the upper part of the cutis. The papillary bodies are elongated, corresponding to the downward growth of the rete pegs. Slight vascular dilatation, mild interstitial edema and a moderate small round and plasma cell infiltration is seen throughout the upper part of the cutis. Basophilic degeneration is usually present in the subepidermic region (figs. 8 and 9).

A malignant condition frequently develops from this form of senile keratosis, even prior to the development of a senile verruca or senile acanthoma. Prickle cell epithelioma is most usual; however,

Bowen type change or epithelioma of basal cell or anaplastic cell type are seen at times.

The flat type of senile keratosis is found on the vermilion border of the lips, ears, face, forehead and dorsa of the hands. These lesions

Fig. 10.—There is large irregular senile keratosis of the flat type on the face.

Fig. 11.—This is the flat type of senile keratosis, showing acanthosis and hyperkeratosis. In the lower portion of the epidermis are large cells. Beneath the keratosis is an intense cellular infiltration (× 72.8).

conform more to true keratoses than the others in this group, as the surface is smooth, flat and not verrucous, as well as covered with hyperkeratosis which may be steatoid, but is usually dry and adherent.

They may be single, but more often multiple, and are irregular in contour. The color may be gray, yellow, brown or sometimes dull red.

The hyperkeratotic layer exfoliates at times, and, accompanying this, superficial erosion or even ulceration may be noted. However, the hyperkeratosis tends to reform. These changes can occur in the absence of malignancy (fig. 10).

Microscopically, in this variety, acanthosis is present but not to a great degree. The epidermis becomes flattened and the rete pegs tend

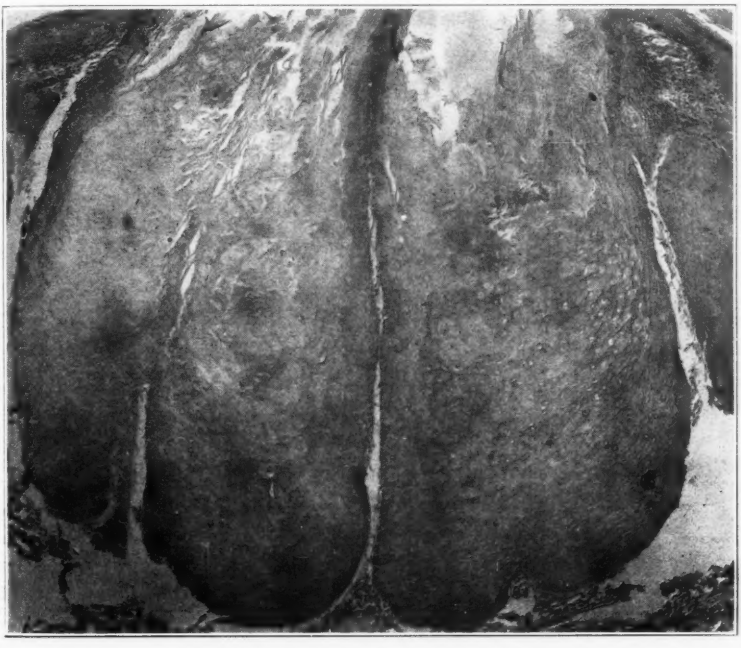

Fig. 12.—This demonstrates a senile verruca, an exaggeration of the papillose type of senile keratosis (× 63).

to be effaced. The stratum corneum is exaggerated, densely packed and often considerably hyperkeratotic. The granular layer is present or increased. Often a varying number of the cells of the lower epidermis and the basal cell margin are somewhat larger and rounder than normal and contain large hyperchromatic nuclei (anaplasia). While the basal cell margin is intact, the normal columnar arrangement of this layer is replaced in part or entirely by these cells.

The upper part of the cutis reveals a moderate to an intense infiltration of small round cells, plasma cells or both. The superficial

vessels are dilated and there is a varying amount of interstitial edema. Basophilic degeneration is a fairly constant observation and may be pronounced (fig. 11).

Anaplastic epithelioma, a highly malignant neoplasm, is the malignant lesion of highest incidence arising from the flat type of senile keratosis. Prickle cell epitheliomas are seen, but we have not observed a basal cell epithelioma developing from this type of keratosis.

SENILE VERRUCA

The term verruca senilis, as previously mentioned, has been used synonomously with seborrheic keratosis and seborrheic verruca. We

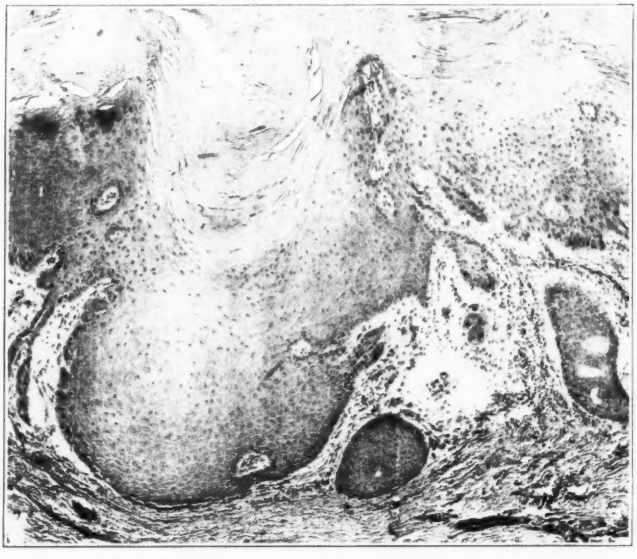

Fig. 13.—A well developed senile acanthoma is present. Above this is a tremendous increase in horny layer. The remainder of the epidermis suggests a possible flat type of senile keratosis (× 63).

prefer to restrict the meaning of senile verruca to those lesions which develop chiefly from the papillose type of senile keratosis. Clinically, this stage is featured by an increase in size, elevation, induration and color of the preexisting keratosis. The resultant clinical picture is that of a prickle cell epithelioma, but the presence or absence of this or any malignant change can be determined only by microscopic examination.

Microscopically, a senile verruca may present an exaggerated picture of the papillose form of senile keratosis. In this event, the acanthotic rete pegs of the keratosis show increased growth (fig. 12).

On the other hand, the acanthosis may extend and force the papillary bodies down, obliterate the rete pegs and form a uniform regular margin, resulting in a well defined localized area of epidermis. This form of senile verruca, which simulates a neoplasm, is called a senile acanthoma (fig. 9). As well as the papillose type, the flat type of senile keratosis may evolve into a senile acanthoma. In this case, a localized area of the epidermis shows increased acanthosis and downward growth (fig. 13).

The surface of senile verruca and senile acanthoma is verrucous. Overlying this is a greatly thickened densely compact hyperkeratosis. Often small areas of the stratum corneum contain nuclei. We believe that this process differs from parakeratosis. The palisade layer is not disturbed, and there is no evidence of malignancy in the epidermis. In the upper and middle part of the cutis the features of inflammation are more pronounced. Considerable basophilic degeneration may be seen.

Prickle cell epithelioma is the commonest malignant neoplasm arising in a senile verruca or acanthoma. Anaplastic epitheliomas are not rare. However, frequently, preceding proliferation and infiltration, the cells of the epidermis show early malignant change. When this occurs, it is impossible to foretell the type of epithelioma that will develop, or, more accurately, it is more difficult to classify this abnormal observation than to describe it as early malignant change.

SUMMARY

Our observations lead us to conclude that there are four types in this group of keratoses: seborrheic keratosis, seborrheic verruca, senile keratosis and senile verruca. Each has its own clinical and microscopic picture. Further, we believe that there are two forms of senile keratoses, the papillose and the flat, and that senile acanthoma is a variety of senile verruca and may arise from either. The clinical and microscopic diagnosis and differentiation of these lesions usually prove comparatively simple, but, occasionally, it may be difficult to distinguish one type from another.

We feel that any of these lesions, at times, may be a forerunner of a malignant condition, but the seborrheic type much less frequently than the senile eventuates in cancer. Certain types of epitheliomas are more apt to form in one member of this group than in another. However, probably any type of epithelial neoplasm may develop in any type of keratosis or verruca.

PITYRIASIS VERSICOLOR

Atypical Clinical and Mycologic Variations

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IT IS only when unusual clinical or mycologic manifestations are present that the diagnosis of pityriasis versicolor (tinea versicolor) is troublesome. The areas most likely to cause difficulty are the neck, scalp, groin and extremities. Mycologic variations occur in patients recently under treatment.

In clinical diagnosis, the use of Wood's light is a valuable adjunct, particularly in determining the extent of involvement. In the laboratory, the etiologic agent is easily determined by direct examination of scales mounted in potassium hydroxide or lactophenol (a mixture of phenol, U.S.P., 20 Gm.; lactic acid, 20 cc.; glycerin U.S.P., 40 cc., and distilled water, 20 cc.). Mounts in lactophenol may be examined immediately, without waiting for clearing. The slide may be sealed with some suitable substance and kept for some time.

Distribution of Lesions of Pityriasis Versicolor in 47 Patients

Site of Lesions	No. of Patients	Per Cent
Classic distribution	45	96
Neck	12	25
Scalp	9	19
Groin	3	6
Thighs	3	6
Face	2	4
Forearm	1	2

CLINICAL OBSERVATIONS

The sites of lesions observed in the 47 cases forming the basis for this study are noted in the accompanying table. The age of the

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patients varied from 19 to 49 years, the greatest number, 37, being from 20 to 29 years of age. Thirteen of the 37 patients were Negroes and 34 were white men.

All the patients with the exception of 2 showed classic distribution of lesions on the upper area of the trunk. One patient revealed lesions only on the right forearm; 1, only on the neck and scalp. Another patient had a large number of lesions on the neck and scalp and a few scattered lesions on the trunk.

The exposed portion of the neck is generally listed as an unusual site, but the results of this study indicate that approximately one fourth of the patients studied had lesions in this area. In all instances, the lesions on the neck were neither so obvious nor so distinct as those on the covered areas of the body. This is to be expected, as the area is exposed to sunlight and trauma from the collar, and more thorough scrubbing of the neck on the part of meticulous persons keeps the lesions at a minimum. Indistinctness of the lesions is especially frequent in fair-skinned persons, in whom inspection alone is often inadequate to establish the diagnosis. It is quite possible that, for these reasons, many cases of involvement of the neck have been overlooked.

Nine of the 12 patients with lesions of the neck (19 per cent of the total patients with pityriasis versicolor) also showed macular lesions of the scalp in the occipital region. Here, the lesions were more erythematous than those of the upper part of the trunk and closely resembled the lesions of seborrheic dermatitis.

Lesions on the back of the neck and on the scalp may be overlooked during examination; as a result, treatment is less thorough and the fungus may persist. The presence of partially treated, or even untreated, lesions may explain the considerable number of cases in which the disease seems, almost inexplicably, to recur.

Involvement of the Groin.—Three cases of this type were noted, all in white patients.

V. J., 25 years old, had incurred the infection three years previously in the South Pacific. He had experienced several recurrent episodes, but the sites of the lesions had been limited to the upper part of the trunk. The patient's first visit to the clinic was made because of the recent spread of the lesions to the area of the groin. Clinical examination revealed macular lesions over the chest, shoulders and back with a few individual macular lesions over the pubic area and the inner portion of the thighs. Microscopic examination disclosed Microsporon furfur in all the areas.

A. B., 27 years old, had incurred the infection three years earlier. Individual maculas were scattered over the upper part of the trunk and over the arms, groin, thighs, back of the neck and occipital region of the scalp.

I. M., 37 years old, stated that his first attack had occurred eighteen months earlier, in France. In addition to a highly generalized involvement of the upper part of the trunk, a type of lesion similar to that of tinea cruris (involve-

ment with uncleared center) was noted. Individual lesions had coalesced to present a rather sharply marginated area on the inner aspect of both thighs, but there were individual and multiple macular lesions throughout the pubic area, over the thighs and over the abdomen. It was difficult to believe that this patient had really incurred the infection not more than eighteen months previously.

Involvement of the Face.—Two patients with pityriasis versicolor of the face were seen. E. B., a 24 year old Negro, had incurred the infection fourteen months earlier, while aboard ship in the South Pacific. Typical macular, furfuraceous patches spread from the apex of the chest over the neck, chin and angle of the jaw, as well as to the occipital region.

R. D. M., a 24 year old white man, presented furfuraceous patches on the face, neck and scalp and typical maculas on the upper part of the back. The infection had been recurrent for four years.

Absence of Fluorescence.—In 1 case, failure of the fungus to fluoresce under Wood's light was noted. We know no explanation for this phenomenon unless there is a strain of M. furfur which does not fluoresce. Slides made from several different areas on the upper portion of the patient's trunk all presented the typical microscopic picture. V. D. C., a white man of 24 years, had incurred the infection two years earlier, in India. He stated that 4 other men with him had contracted the infection about the same time.

MYCOLOGIC OBSERVATIONS

The clusters of budding cells so typical in the scales of pityriasis versicolor are produced by prolific budding on the part of the spherical organisms. They do not appear to be the result of disarticulation of the hyphal elements (arthrospores). The parent organism may produce more than one blastospore at the same time. Although branching mycelium was observed in all the 47 cases studied, it is our opinion that this was pseudomycelium, rather than true mycelium. It was composed of only a few cells and seldom had more than one or two short branches. No blastospores were observed on the pseudomycelium other than young cells believed to be new hyphal elements.

There were several opportunities to make further tests on patients after a regimen of treatment lasting approximately two to three weeks, followed by a lapse of several days without treatment. The medicament employed was a common ointment containing salicylic acid, sulfur and petrolatum. The results of the tests varied from negative to frankly positive (for scales taken from inadequately treated areas). In some of the cases in which there had been response to treatment, there seemed to be a definite change in the organism. No pseudomycelium was observed. Few organisms were present; and these were usually abnormal, having increased to two or three times their normal size without budding, and were less refractory than the cells in untreated lesions.

SUMMARY

Uncommon clinical manifestations of pityriasis versicolor (tinea versicolor) are described.

The presence of undiagnosed and untreated lesions of the neck and scalp may serve as a focus of persistent and recurrent episodes of pityriasis versicolor.

Mycologic observations on treated and untreated patients are noted.

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DERMATOMYOSITIS

Report of Three Cases with Postmortem Observations

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AND
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DERMATOMYOSITIS, although predominantly a disease of the skin and skeletal muscle, may affect many other organs. It may, therefore, be regarded as a systemic disease.

In this paper the observations at autopsy in 3 patients with dermatomyositis will be reviewed and emphasis will be placed on the lesions which were found in organs other than the skin and skeletal muscles. Pathologic changes attributable to dermatomyositis were observed in the heart muscle, the subcutaneous and visceral fat and the intestines. The resemblance of the histologic changes in dermatomyositis to those of lupus erythematosus and scleroderma will be commented on.

REPORT OF CASES

CASE 1.—(This case was presented at one of the Weekly Clinicopathological Exercises of the Massachusetts General Hospital.[1]) The patient, a 54 year old nurse, began to feel weak in September 1942. In December an erythematous eruption developed on the back of the neck and at the base of the finger nails. The eruption gradually spread to the face and arms. In January 1943 dysphagia developed.

On admission, on Jan. 24, 1943, the patient appeared acutely ill. There was edema of the periorbital regions, the hands and forearms. A diffuse erythema extended over the face, neck and chest. The hands, forearms, shoulders and abdomen showed a red papular eruption. There was generalized muscular weakness. The muscles of the neck and arms were tender to pressure. Examination of the heart revealed a soft blowing systolic murmur over the entire precordium.

Over a period of several months after admission the extreme weakness and muscle tenderness persisted. Six months after admission the patient began to have cramping abdominal pains and diarrhea. Results of guaiac tests of the stools were positive. On proctoscopic examination a small punched-out ulcer was found on the anterolateral wall of the rectum. A biopsy of the ulcer revealed acute inflammation. Following this episode the patient improved, and she was discharged to a nursing home on October 1.

The patient was readmitted on November 5 because of vomiting, alternating diarrhea and constipation and severe pain in the lower part of the abdomen.

From the Departments of Dermatology and Pathology, Massachusetts General Hospital.

1. Weekly Clinicopathological Exercises, Cabot Case 31101, New England J. Med. **232**:286, 1945.

Roentgenograms showed dilatation, gross segmentation, mucosal irregularities and loss of mucosal pattern throughout the small bowel. Hourly roentgenograms following a barium sulfate meal revealed a slight delay in transit through the small intestines. These changes were considered suggestive of scleroderma or dermatomyositis.

An electrocardiogram on November 7 showed, in the standard leads, low voltage of the T waves and of the QRS complexes. In the standard leads the T waves were upright, but they were deeply inverted in lead CF_4. Dr. Conger Williams of the Department of Medicine, Massachusetts General Hospital, stated that this pattern suggested widespread myocardial involvement.

The patient died on November 18, after an illness of fourteen months' duration.

Postmortem Observations.—All muscles were greatly diminished in volume. They were pale, with a slight yellow tinge. The mucosa of the lower part of the esophagus revealed a few round punched-out ulcers, averaging 0.3 cm. in diameter. Approximately 2,500 cc. of thick yellow purulent fluid was present in the peritoneal cavity. The entire intestinal wall was edematous, thick and brawny and exuded a mucoid material. Scattered throughout the entire jejunum were sharply punched-out ulcers, some of which were minute while others measured up to 1 cm. in diameter. Several of these ulcers had perforated. A few ulcers were present in the rectum.

Microscopic Examination: Sections of the skin revealed an atrophic epidermis. There was edema of the upper part of the corium. The collagen fibers showed fragmentation and, in some areas, basophilic degeneration. Several capillaries showed edema of their walls. There was focal fibrosis of the subcutaneous fat, with degeneration and breaking up of the fat cells. Islands of calcification were present deep in the subcutaneous fat. Neither the skin nor the subcutaneous fat showed any appreciable amount of inflammatory infiltrate.

Sections of skeletal muscle showed extensive degeneration and replacement by fibrous tissue. A moderate amount of edema and inflammatory infiltrate were present in most areas of degeneration. The heart showed pronounced interstitial edema of the myocardium.

Sections of the ileum, jejunum and colon showed decided edema of the walls, particularly in the submucosa. The serosa was covered with a fibrinopurulent exudate. Many of the large and medium-sized arteries showed pronounced mucoid and fibrous intimal thickening with narrowing of their lumens (fig. 1). Many vessels contained recent or organized thrombi. Occluded vessels were present at the base of each of the mucosal ulcers (fig. 2). A few of the arteries in the periadrenal fat showed fibrous thickening of the intima.

CASE 2.—The patient, a 63 year old Portuguese metal worker, first noted, in April 1943, an erythematous eruption on his face and on the backs of his hands. In July edema of the face, neck and arms developed, and the patient began to complain of weakness of the muscles of the shoulders and legs.

Examination on admission, on August 22, revealed diffuse erythema and considerable edema of the face, neck, upper part of the chest, arms and hands. There were general weakness and loss of muscle tone.

An electrocardiogram showed low T waves in leads 1, 2 and 3. Lead 3 showed, in addition, slight sagging S-T segments. There was a tendency to right axis deviation. Dr. Conger Williams interpreted the electrocardiogram as a borderline record. He stated that the abnormality in the T waves could be produced by a generalized myocardial involvement such as that seen in dermatomyositis.

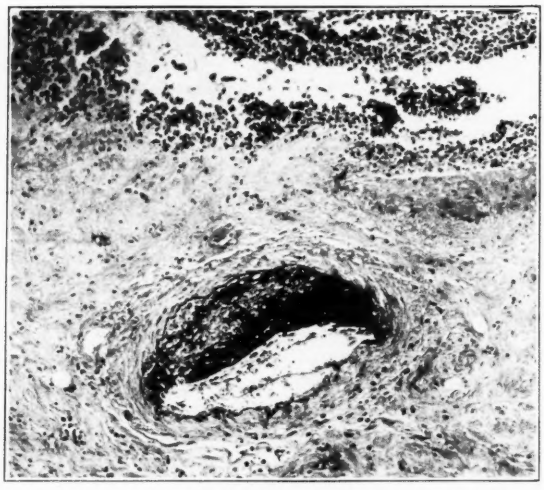

Fig. 1 (case 1).—A section of the small intestine shows mucoid and fibrous thickening of the intima of an artery at the base of a mucosal ulcer (× 200).

Fig. 2 (case 1).—A section of the small intestine shows occluded and thickened blood vessels at the base of a mucosal ulcer (× 50).

but that other factors, like anemia, malnutrition and cachexia, could produce similar electrocardiographic changes.

The patient's condition deteriorated rapidly. Dysphagia and extensive subcutaneous edema developed. The patient died on September 14, five months after the onset of his illness.

Postmortem Observations.—The entire body surface was doughy to palpation, because of the presence of nonpitting edema. Nearly all muscles, including those of the tongue, were swollen, boggy and pale. The pectoral muscles were extremely atrophic. The lower lobes of both lungs showed bronchopneumonia.

Microscopic Examination: Sections of the skin showed atrophy of the epidermis with hyperkeratosis and follicular plugging. In the upper third of the corium

Fig. 3 (case 2).—The heart muscle shows interstitial edema and an inflammatory infiltrate between the muscle fibers (× 100).

focal infiltrates of monocytes and lymphocytes were present around many of the capillaries. The lower part of the corium showed severe degeneration of the collagen and of the elastic fibers. Both were fragmented and stained basophilic in part. The subcutaneous fat showed considerable variation in the size and shape of the fat cells, slight fibrosis and focal lymphocytic infiltration. Some of the arterioles and venules of the subcutaneous fat showed moderate edema of their walls, particularly of the intima.

Sections of skeletal muscle revealed widespread degenerative and inflammatory changes consistent with dermatomyositis. The muscles of the esophagus and tongue showed the same changes as the skeletal muscles, but to a lesser degree. There was basophilic degeneration of the collagen between the epithelium and the muscle layers of both the tongue and the esophagus. The heart muscle was normal

except in the sections of one block, in which there was edema separating the muscle fibers and a moderate amount of infiltrate composed of lymphocytes and monocytes between the muscle fibers (fig. 3). In some areas the infiltrate was perivascular in arrangement.

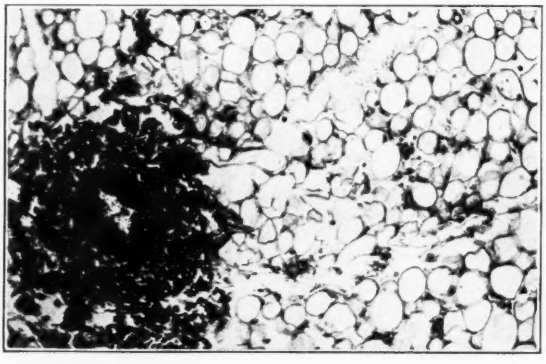

Fig. 4 (case 3).—A section of subcutaneous fat shows mucoid degeneration of the fat cells. No inflammatory reaction is present. The blood vessel shows fibrous thickening (× 100).

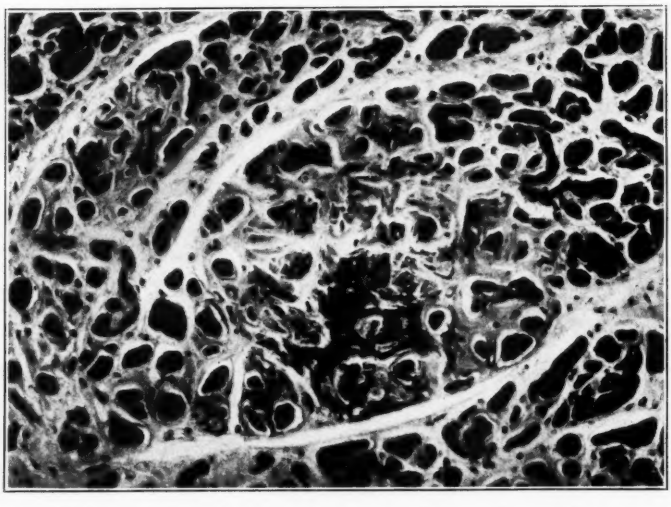

Fig. 5 (case 3).—The heart muscle shows a focus of mucoid degeneration (× 400).

The subepicardial and periadrenal fat tissue showed variation in the size and shape and breaking up of fat cells. There was focal as well as diffuse round cell infiltration. The spleen showed congestion and hemorrhage into the pulp.

CASE 3.—(This case is presented with the permission of Dr. Francis G. Barnum.) The patient, a 76 year old painter, had been in good health until June 16, 1942. That morning he noted pain and weakness in the left shoulder. Four days later the right shoulder became similarly affected, and his voice became weak and nasal. Physical examination eight days after the onset of symptoms showed swelling of the arms and forearms. The patient was unable to raise his arms, because of muscular weakness.

The patient's condition deteriorated rapidly. An erythematous eruption developed in the malar regions and on the chest. The weakness extended to many other muscle groups, and dysphagia developed. The patient died three months after the onset of symptoms.

Postmortem Observations.—The body showed considerable emaciation. The skeletal muscles were thin and soft. The heart showed diffuse thickening of the endocardium of the left ventricle. The lungs showed extensive bronchopneumonia.

Fig. 6 (case 3).—A section of the heart muscle shows, directly beneath the endocardium, diffuse mucoid degeneration of the interstitial tissue surrounding, compressing and apparently producing degeneration of individual myocardial fibers (× 200).

Microscopic Examination: Sections from the skin showed atrophy of the epidermis, with hyperkeratosis and moderate follicular plugging. In the upper third of the corium the collagen fibers were fragmented. The collagen bundles of the lower part of the corium were thickened and coarser than normal. Several of the arterioles and venules of the corium and subcutaneous fat showed thickening of their walls, particularly of their intima, and were surrounded by a chronic inflammatory infiltrate. Thick strands of collagen extended from the corium into the subcutaneous fat, dividing the fat into lobules. In many areas the fat cells were irregular in size and shape. Scattered throughout the subcutaneous fat there were areas in which pale-staining mucoid material was interspersed between the fat cells and partially or completely filled the fat cells (fig. 4).

Sections of skeletal muscle showed extensive areas of degeneration and a scattered infiltrate of lymphocytes and monocytes, particularly about the arterioles.

Sections of muscle from the larynx and trachea presented moderate edema and small foci of lymphocytes and monocytes. The heart showed multiple foci of mucoid degeneration of the interstitial connective tissue. The mucoid material surrounded, compressed and apparently produced degeneration of individual myocardial fibers (figs. 5 and 6). In addition there were a few areas in which inflammatory cells were interspersed between the muscle bundles. The endocardial connective tissue of the left ventricle was increased in amount and showed fibrosis.

The fat tissue around most organs, but particularly the subcutaneous, perimuscular and periadrenal fat, showed atrophy and mucoid degeneration of the fat cells, a diffuse inflammatory infiltrate and fibrous replacement. Several of the blood vessels in the periadrenal fat showed subintimal thickening, and a few of these vessels also showed mucoid degeneration of the intima (fig. 7). The stomach showed an undifferentiated carcinoma with metastases to the regional lymph nodes.

Fig. 7 (case 3).—A section of the periadrenal fat shows degeneration of the fat cells with slight diffuse inflammation. The walls of the blood vessels show mucoid degeneration and fibrous thickening (× 200).

COMMENT ON THE VISCERAL LESIONS IN DERMATOMYOSITIS, WITH REVIEW OF THE LITERATURE

Pathologic changes were found in the skin, the skeletal muscle, the heart and the fat depots of all 3 patients and in the intestines of 1 patient.

Skin and Skeletal Muscle.—The histologic changes in the skin and skeletal muscles corresponded to those described in the literature.[2]

Heart Muscle.—Histologic changes in the heart muscle have been frequently reported. These changes have been described as being

2. (*a*) Kinney, T. D., and Maher, M. M.: Dermatomyositis: A Study of Five Cases, Am. J. Path. **16**:561 (Sept.) 1940. (*b*) O'Leary, P. A., and Waisman, M.: Dermatomyositis: A Study of Forty Cases, Arch. Dermat. & Syph. **41**:1001 (June) 1940.

identical with those found in the skeletal muscle but less severe.[3] The muscle fibers may show focal degenerative changes, such as granular degeneration,[4] loss of striation,[5] vacuolization [5] and necrosis.[3d] In addition to degeneration, there may be fibrosis.[6] There is occasionally edema of the muscle fibers [7] or interstitial edema.[8] The involved areas may show an inflammatory infiltrate between the muscle fibers.[2] The capillaries, arterioles and venules of the myocardium may also be involved. The process may consist of dilatation of these vessels,[9] hyalinized thickening of their walls with resulting narrowing of the lumens [2a] and occlusion by fibrous thrombi.[7b] Lorenz [10] has described hemorrhages in the heart muscle.

Histologic Changes, Aside from Those in the Skin and Muscle, in 3 Cases of Dermatomyositis

	Heart	Fat Depots	Intestinal Tract
Case 1.....	Interstitial edema	Subcutaneous fat: Fibrosis Degeneration of fat cells Calcification	Mucoid and fibrous thickening of the intima and thrombosis of the small arteries of the jejunum and rectum, most pronounced at the bases of mucosal ulcers
Case 2.....	Interstitial edema with foci of inflammation	Subcutaneous, subepicardial and periadrenal fat: Degeneration of fat cells Inflammatory infiltrate	
Case 3.....	Foci of mucoid degeneration and foci of inflammation	General involvement of fat: Mucoid degeneration Inflammatory infiltrate Fibrous replacement	

3. (*a*) Kinney and Maher.[2a] (*b*) O'Leary and Waismen.[2b] (*c*) von Kornilow, A.: Polymyositis primaria acuta, Deutsche Ztschr. f. Nervenh, **9**:119, 1897. (*d*) von Zalka, E.: Ueber einen seltsamen Fall von Polymyositis, Virchows Arch. f. path. Anat. **281**:114, 1931. (*e*) Schmautzer, J.: Ueber Polymyositis acuta, Med. Klin. **10**:281, 1914.

4. Lamb, J. H.: Dermatomyositis, J. Oklahoma M. A. **37**:5 (Jan.) 1944.

5. (*a*) von Kornilow.[3c] (*b*) Schulz, R.: Sclerodermie, Morbus Addisonii und Muskelatrophie, Neurol. Zentralbl. **8**:345, 386 and 412, 1889.

6. (*a*) Kinney and Maher.[2a] (*b*) Frazer, M. J. L.: Case of Dermatomyositis, Brit. J. Dermat. **54**:265 (Oct.) 1942.

7. (*a*) Schulz.[5b] (*b*) Ingram, J. T., and Stewart, M. J.: Dermatomyositis and Poikilodermia, Brit. J. Dermat. **46**:53 (Feb.) 1934.

8. (*a*) Kinney and Maher.[2a] (*b*) Schmautzer.[3e] (*c*) Schulz.[5b] (*d*) Greenaway, T. M., and Lambie, C. G.: Dermatomyositis, Brit. J. Dermat. **49**:209 (May) 1937.

9. Köster, H.: Zur Kenntnis der Dermatomyositis, Deutsche Ztschr. f. Nervenh. **12**:150, 1898.

10. Lorenz, H.: Dermatomyositis, Berl. klin. Wchnschr. **43**:727, 1906.

We observed changes in the heart muscle in all 3 cases (table). In 2 cases the changes were slight. They consisted of interstitial edema in 1 case (case 1) and of interstitial edema associated with focal inflammation in the other (case 2). One patient (case 3) presented foci of mucoid degeneration of the interstitial connective tissue scattered throughout the myocardium, slight chronic inflammation between the muscle bundles and fibrosis of the endocardial connective tissue.

Fat Depots.—Pathologic changes in the subcutaneous fat have been described as consisting of edema of the subcutaneous fat,[11] mucoid degeneration,[2a] hyaline degeneration,[12] round cell infiltration,[13] fibrous tissue replacement[14] and calcification.[15] Changes in other than subcutaneous fat depots have been reported by Kinney and Maher,[2a] who found an infiltrate composed of lymphocytes and a few polymorphonuclear leukocytes in the subepicardial fat in 1 case.

Pathologic changes in the fat were encountered in all 3 of our cases. In case 1 the subcutaneous fat only was involved. In case 2 the subepicardial and periadrenal fat were also affected, while case 3 showed general involvement of the fat. The changes in the fat were characterized by variation in size and shape and breaking up of the fat cells, a diffuse lymphocytic infiltrate and partial fibrosis. In 1 case (case 3) the fat cells presented, in addition, mucoid degeneration in which pale-staining mucoid material was present between the fat cells and partially or completely replaced some of the fat cells. In 1 instance (case 1) foci of calcification were present in the subcutaneous fat. One case (case 3) showed changes in the blood vessels of the periadrenal fat, consisting of subintimal thickening of the arterioles and mucoid degeneration of the intima of some of these vessels.

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11. (*a*) Greenaway and Lambie.[8d] (*b*) Steinitz, H., and Steinfeld, F.: Untersuchungen zum Kreatinstoffwechsel bei Dermatomyositis, Ztschr. f. d. ges. exper. Med. **79**:319, 1931. (*c*) von Niedner: Dermatomyositis und infektiöse Muskelerkrankungen, Deutsche med. Wchnschr. **46**:570, 1920.

12. Weber, F. P., and Gray, A. M. H.: Chronic Relapsing Polydermatomyositis with Predominant Involvement of the Subcutaneous Fat (Panniculitis), Brit. J. Dermat. **36**:544 (Dec.) 1924.

13. Kinney and Maher.[2a] Greenaway and Lambie.[8d] von Niedner.[11c]

14. (*a*) Kinney and Maher.[2a] (*b*) Greenaway and Lambie.[8d] (*c*) Marcus, I. H., and Weinstein, J.: Dermatomyositis: Report of a Case with a Review of the Literature, Ann. Int. Med. **9**:406 (Oct.) 1935. (*d*) Batten, F. E.: Case of Dermatomyositis in a Child with Pathological Report, Proc. Roy. Soc. Med. (Sect. Neurol.) **5**:103, 1911-1912. (*e*) Brock, W. G.: Dermatomyositis and Diffuse Scleroderma: Differential Diagnosis and Reports of Cases, Arch. Dermat. & Syph. **30**:227 (Aug.) 1934.

15. (*a*) Brock.[14e] (*b*) Horn, R. C. Jr.: Poikilodermatomyositis: Report of a Case with Complete Postmortem Examination, Arch. Dermat. & Syph. **44**:1086 (Dec.) 1941.

Intestinal Tract.—Intestinal lesions have, so far, been reported in 9 cases of dermatomyositis. The first 2 cases [16] are inconclusive, since the data are insufficient. In two subsequent reports the presence of intestinal ulcers at autopsy was recorded. The authors, however, did not regard the ulcers as caused by dermatomyositis. Janowsky [17] found multiple ulcers in the duodenum, which he considered incidental. Moore and Koch [18] found ulcers in the stomach and small intestines which, on microscopic examination, revealed thrombosed arterioles in the submucosa at the center of the ulcers. The authors ascribed these changes to infected emboli which, by occlusion of the vessels, had caused the mucosal ulcerations.

Karelitz and Welt,[19] in 1932, were the first to attribute intestinal ulcerations observed on autopsy to dermatomyositis. In their case the intestinal ulcerations were associated with vascular lesions consisting of edema and round cell infiltration of the vascular walls. Marcus and Weinstein [14c] noted ulcerations of the esophagus and large intestine. The ulcers showed only chronic inflammatory changes at their bases without vascular lesions. Horn [15b] reported a case of dermatomyositis with multiple ulcers in the esophagus and duodenum. Histologic examination of the ulcers revealed a necrotizing inflammatory process involving both arteries and veins. In addition there were a few thick-walled hyalinized arterioles scattered throughout the gastrointestinal tract. Schuermann [20] found ecchymoses with central necrosis in the gastric mucosa and erosions in the lower portion of the small intestines. Histologic sections showed no vascular changes. Kinney and Maher [2a] found the mucosa of the duodenum and of the jejunum diffusely reddened in 1 case. Histologic examination revealed vascular changes in the intestinal wall, consisting of perivascular infiltration by lymphocytes and polymorphonuclear leukocytes and of thrombosis of a few vessels. The authors noted, however, that these changes were most pronounced at sites in the duodenum and jejunum in which several ascarides were seen.

One of our cases (case 1) showed pronounced vascular changes in the jejunum and rectum (table). The process involved the small

16. (*a*) Potain: Morve chronique de forme anormale, Bull. et mém. Soc. méd. d. hôp. de Paris **12**:314, 1875. (*b*) Buss: Ein Fall von acuter Dermatomyositis, Deutsche med. Wchnschr. **20**:788, 1894.

17. Janowsky, T. G., and Wyssokowicz, W. K.: Ein Fall von Dermatomyositis, Deutsches Arch. f. klin. Med. **71**:493, 1901.

18. Moore, C., and Koch, L. A.: Dermatomyositis: Report of a Case with Necropsy, Am. J. Dis. Child. **35**:71 (Jan.) 1928.

19. Karelitz, S., and Welt, S. K.: Dermatomyositis, Am. J. Dis. Child. **43**: 1134 (May) 1932.

20. Schuermann, H.: Zur Klinik und Pathogenese der Dermatomyositis (Polymyositis), Arch. f. Dermat. u. Syph. **178**:414, 1939.

arteries and consisted of mucoid and fibrous thickening of the intima with narrowing of the lumen. Many of the vessels were thrombosed. These vascular changes were most pronounced at the bases of the ulcers and, therefore, can be regarded as responsible for the mucosal ulcerations and perforations.

Serous Membranes.—Involvement of the serous membranes in dermatomyositis has been reported as consisting of serofibrinous peritonitis,[21] pleuritis[22] and pericarditis.[23] Petechiae in the pleura,[24] peritoneum[17] and pericardium[25] have been described. In 1 case[6b] lymphocytic infiltration of the epicardium was noted. Increase in the amount of synovial fluid[22d] and thickening of the synovia in the knee joints[26] have also been reported.

Kidneys.—Renal lesions which could be directly attributed to dermatomyositis have not been reported so far.

Spleen.—The gross observation of an enlarged spleen in dermatomyositis has been reported by many authors.[27] No histologic changes in the spleen which could be specifically related to dermatomyositis have been reported.

Liver.—Parenchymatous degeneration and fatty infiltration of the liver have been described by many authors.[28] Since dermatomyositis is a severe debilitating disease such changes are probably only a secondary manifestation. In 2 reported cases[29] the interstitial tissue showed infiltration with leukocytes and round cells.

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21. Kinney and Maher.[2a] Janowsky and Wyssokowicz.[17]

22. (*a*) Kinney and Maher.[2a] (*b*) Marcus and Weinstein.[14c] (*c*) Janoswsky and Wyssokowicz.[17] (*d*) Jollasse, O.: Ueber acute primäre Polymyositis, Mitt. a. d. Hamb. Staatskrankenanst. **1**:326, 1897. (*e*) Wolf, A., and Wilens, S. L.: Dermatomyositis: A Report of Two Cases with Complete Autopsy, Am. J. Path. **12**:235 (March) 1936. (*f*) Davison, C.: Dermatomyositis: A Clinicopathologic Study; Report of a Case with Complete Necropsy, Arch. Dermat. & Syph. **19**:255 (Feb.) 1929.

23. Kinney and Maher.[2a] Janowsky and Wyssokowicz.[17] Jollasse.[22d]

24. Kinney and Maher.[2a] Potain.[16a]

25. O'Leary and Waisman.[2b] Jollasse.[22d] Moore and Koch.[18]

26. (*a*) Jollasse.[22d] (*b*) Fahr, T.: Zur Frage der Polymyositis, Arch. f. Dermat. u. Syph. **130**:1, 1921.

27. (*a*) Kinney and Maher.[2a] (*b*) O'Leary and Waisman.[2b] Schuermann.[20] (*d*) Fahr.[26b] (*e*) Sheldon, J. H.; Young, F., and Dyke, S. C.: Acute Dermatomyositis, Lancet **1**:82 (Jan. 14) 1939. (*f*) Gwynn, N. C., and Gordon, W.: A Case of Dermatomyositis Which Recovered, ibid. **2**:226, 1910. (*g*) Bronson, E.: Case of Dermatomyositis, Proc. Roy. Soc. Med. (Sect. Dis. Child.) **10**:28, 1916-1917.

28. Lamb.[4] Steinitz and Steinfeld.[11b] Marcus and Weinstein.[14c] Batten.[14d] Karelitz and Welt.[19] Fahr.[26b] Hecht, M. S.: Dermatomyositis in Childhood, J. Pediat. **17**:791 (Dec.) 1940.

29. Schulz.[5b] Moore and Koch.[18]

Thyroid.—Dowling [30] has stated that the thyroid gland is rather frequently involved in dermatomyositis. He stated that in cases in which the disease was rapidly fatal there was colloid goiter with increase in stroma, while in cases of chronic disease there was atrophy of the glandular tissue with interstitial fibrosis. Frazer [6b] found the thyroid gland small and fibrotic, the acini lined by flat epithelium and distended with colloid.

Adrenals.—The adrenals have been described as reduced in size,[6b] as showing parenchymatous degeneration [14c] or as showing focal degeneration.[5b]

Pancreas.—The pancreas has been described as showing parenchymatous degeneration.[14c]

COMMENT

It is evident from our postmortem observations and those reported in the literature that dermatomyositis may affect many other organs besides the voluntary musculature and the skin. In our 3 cases the changes observed in the heart, the fat and the blood vessels were characterized by degeneration with little or no inflammation. In areas in which the degeneration was severe, it was mucoid in type.

Two observations in relation to the heart lesions are noteworthy: First, in cases 1 and 2 the histologic changes in the myocardium were mild, while electrocardiographic studies suggested generalized myocardial damage. This suggests that in dermatomyositis damage to the tissue may be severer than histologic methods indicate. Second, in case 2, in which many blocks of heart muscle were examined, only one area of one block showed evidence of myocarditis. This indicates that the lesions of dermatomyositis may be focal. In order not to miss such areas it is advisable to examine numerous blocks of those organs in which lesions are suspected.

Analysis of the microscopic changes observed in dermatomyositis has convinced us that inflammation is not the primary alteration and cannot be held responsible for the degenerative lesions. Neither are vascular changes the cause of the degeneration, since they are often absent and, when present, are usually mild. Thus it appears that degeneration represents the basic morphologic alteration in dermatomyositis. This degeneration affects muscle and collagen. Inasmuch as fatty tissue is a modified collagen and the vascular wall contains collagen, the changes in the body fat and in the blood vessels can be regarded as caused by collagen degeneration. Fibrosis which occurs especially in the skin and in the muscles most likely represents a reparative process. It may, in some instances, represent an attenuated response to the same damaging agent that usually causes degeneration.

30. Dowling, G. B.: Generalized Scleroderma, Brit. J. Dermat. **52**:242 (Aug.-Sept.) 1940.

Some of the histologic changes in our cases closely resemble those observed in systemic lupus erythematosus and diffuse scleroderma. The histologic changes observed in some of the sections from the skin resembled those of lupus erythematosus, since they showed hyperkeratosis with follicular plugging, atrophy of the epidermis and degeneration of the collagen. Furthermore, degeneration and inflammatory changes in the muscles and in the fat occur both in dermatomyositis and in systemic lupus erythematosus, although they are less pronounced in lupus erythematosus. The fibrosis observed in some of the sections of skin, muscle and fat was indistinguishable from that occurring in diffuse scleroderma. The intimal edema and fibrosis which occurred in some of the smaller vessels of the skin, the fat depots and the intestines are also a common observation in diffuse scleroderma.

Klemperer, Pollack and Baehr [31] originally established the concept that widespread degeneration of collagen forms the morphologic basis for the lesions in disseminated lupus erythematosus and surmised that scleroderma may be due to the same process. We believe that dermatomyositis is related to these two diseases as suggested by Pollack,[32] Baehr [33] and Banks.[34] Widespread degeneration of collagen seems to represent the common morphologic background of these three conditions. In dermatomyositis the degeneration is severe and usually provokes a pronounced inflammatory reaction, especially in the muscles. In diffuse scleroderma the degeneration is mild and is accompanied with only slight inflammation, but it is followed by pronounced fibrosis. In systemic lupus erythematosus the degeneration occurs in innumerable widely scattered small foci and is accompanied with a mild inflammatory reaction.

SUMMARY

Postmortem studies of 3 cases of dermatomyositis revealed the presence of lesions not only in the skin and skeletal muscle but also in other organs. Lesions were observed in the heart and the body fat in all 3 cases and in the intestines in 1 case.

It is our belief that degeneration of muscle tissue and collagen represents the basic morphologic alteration in dermatomyositis and that inflammation is secondary. Dermatomyositis is probably related to diffuse scleroderma and to systemic lupus erythematosus. Degeneration of collagen seems to represent the basic lesion in all three diseases.

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31. Klemperer, P.; Pollack, A. D., and Baehr, G.: Pathology of Disseminated Lupus Erythematosus, Arch. Path. **32**:569 (Oct.) 1941.

32. Pollack, A. D.: Visceral and Vascular Lesions in Scleroderma, Arch. Path. **29**:859 (June) 1940.

33. Baehr, G., in discussion on Pollack.[32]

34. Banks, B. M.: Is there a Common Denominator in Scleroderma, Dermatomyositis, Disseminated Lupus Erythematosus, the Libman-Sachs Syndrome and Polyarteritis Nodosa? New England J. Med. **225**:433 (Sept. 18) 1941.

INFLAMMATORY RINGWORM DUE TO TRICHOPHYTON FAVIFORME

Report of Seventeen Cases

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INASMUCH as most mycologic studies are carried out in urban areas, it seems possible that the incidence of infections due to the various species of dermatophytes may differ in rural practice and, indeed, may vary with the section of the country studied. Ringworm in rural areas is usually of animal origin, inflammatory on the smooth skin and kerion-like in the beard and scalp. Fowle and Georg [1] in 1947 reported 14 cases of suppurative ringworm due to the faviform trichophyton, and it now seems apparent that this organism may assume considerable importance as a cause of ringworm of animal origin. Until 1942 it had been isolated but once in the United States, that instance being in the case reported by Gammel and Work [2] in 1938. Most reports point to Microsporum felineum (lanosum) as the organism most commonly causing inflammatory ringworm, with Microsporum gypseum (fulvum) reported less commonly.[3] Among the trichophyta only Trichophyton mentagrophytes (gypseum group) has been important in the American literature. [4] Since Sabouraud,[5]

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Dr. Rhoda W. Benham and Dr. Lucille K. Georg of the Department of Dermatology, College of Physicians and Surgeons, Columbia University, and Dr. Albert P. McKee of the Department of Bacteriology, College of Medicine, State University of Iowa, gave aid and guidance in the work preliminary to the writing of this paper. Miss Mary E. Hopper of the Department of Medicine, Cornell University Medical School, and Dr. Norman F. Conant of the Department of Bacteriology, Duke University Medical School, in addition to the aforementioned persons, aided in the identification of the first cultures.

1. Fowle, L. P., and Georg, L. K.: Suppurative Ringworm Contracted from Cattle, Arch. Dermat. & Syph. **56**:780-793 (Dec.) 1947.

2. Gammel, J. A., and Work, J. L.: Sycosis Parasitica Due to Favotrichophyton Album Var. Singulare, Arch. Dermat. & Syph. **38**:756-772 (Nov.) 1938.

3. Lewis, G. M., and Hopper, M. E.: An Introduction to Medical Mycology, ed. 2, Chicago, The Year Book Publishers, Inc., 1943.

4. Lynch, F. W.: Ringworm of the Scalp (Tinea Capitis), Journal-Lancet **65**:228-229 (June) 1945. Laymon, C. W.: Ringworm of the Scalp, Minnesota Med. **28**:363-367 (May) 1945. Levin, O. L., and Behrman, H. T.: The Problem of Nonfluorescent Ringworm of the Scalp: A Warning, J. A. M. A. **128**:350-352 (June 2) 1945.

(Footnotes continued on next page)

in 1893, first recognized the faviform trichophyta, later collecting a total of 9 cases, it has been reported in more or less isolated instances from various parts of the world.[6] Georgjević and Milochevitch [7] found 81 cases of the infection in Yugoslavia, and from Canada 28 cases, 9 proved by culture, were reported by Davidson and his co-workers.[8] Burgess [9] described 1 case of tinea barbae and 1 of tinea circinata due to faviform trichophyta out of 99 cases of fungous infections of the scalp, beard and glabrous skin.

Since the presence of human infections with Trichophyton faviforme was discovered in Iowa in 1946, certain changes in the routine methods of isolation have made apparent a remarkable preponderance of infections due to this organism. Three factors have made difficult the isolation of T. faviforme: First, infections due to this organism often have large numbers of secondary bacterial invaders present; second, its slow growth prevents it from outstripping bacteria and nonpathogenic fungi on the culture plate, and, third, incubation at 37 C., ideal for this organism, was not routine in cases of inflammatory ringworm.

During the past two years 39 cases of inflammatory ringworm of the scalp, beard and glabrous skin have been studied by cultural methods in the department of dermatology in the University Hospitals. For purposes of this paper, inflammatory ringworm of the glabrous skin is considered to present oozing, vesiculation or pustulation in addition to erythema. Where the disease in any particular patient involved more than one of the three general sites listed, such as beard and scalp or scalp and glabrous skin, only the most severely involved site is used for statistical purposes. The table provides a breakdown of the results of mycologic studies on these patients.

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5. Sabouraud, R.: Contribution à l'étude de la trichophytie humaine, Ann. de dermat. et syph. **4**:814-835, 1893. Sabouraud, R.: Les trichophyton faviformes, ibid. **9**:609-635, 1908. Darier, J., and others: Nouvelle pratique dermatologique, Paris, Masson & Cie, 1936, vol. 2.

6. Carol, W. L. L.: A Case of Infection with Trichophyton Faviforme Album and a Case of Infection with Microsporon Orientale (New Species), Urol. & Cutan. Rev. **32**:19-23 (Jan.) 1938. Rossetti, N.: Trichophyton Album (Sabouraud, 1909): A Clinical Case and Cultural Mycologic Study on a Medium with Staphylococci as Base, An. brasil. de dermat. e sif. **20**:155-170 (June) 1945. Thomas, B. A.; Lennox, M., and Duncan, J. T.: The Role of Animal-Type Dermatophytes in Human Ringworm, Brit. M. J. **2**:346-349 (Sept. 15) 1945.

7. Georgejević, G., and Milochevitch, S.: Aspects cliniques de trichophytie et de favus provoqués par le Trichophyton faviforme album, Ann. de parasitol. **13**:243-252 (May) 1935.

8. Davidson, A. M.; Gregory, P. H., and Birt, A. R.: Clinical and Mycological Study of Suppurative Ringworm, Canad. M. A. J. **31**:587-591 (Dec.) 1934.

9. Burgess, J. F.: Fungus Infections of the Skin: A Report on Cultural Study of Flora of Ringworm, Arch. Dermat. & Syph. **12**:853-857 (Dec.) 1925.

Thus, out of 39 patients studied, thirty-two pathogenic fungi were cultured, of which seventeen were T. faviforme. In addition, in 3 patients from whom the causative agent was not isolated, the direct examination of the infected hairs was strongly suggestive of the same infection. No attempt has been made to classify further the faviform trichophyta since both Trichophyton album and Trichophyton discoides forms have been noted, not only in consecutive subcultures but in sectors of the same colony. Trichophyton ochraceum has not been seen. Georg,[10] using single spore cultures, has demonstrated that T. album, T. discoides and T. ochraceum are all variants of a single species, T. faviforme. The animal microspora were far less important causes of tinea capitis in these cases than in series reported from other areas, and the infection in both cases due to M. felineum was acquired outside Iowa, in 1 case from California and in 1 from Texas. In all

Results of Cultures in Cases of Inflammatory Ringworm

Organism	Tinea Capitis	Tinea Barbae	Tinea Glabrosa	Total
Trichophyton faviforme	9	2	6*	17
Trichophyton mentagrophytes (gypseum group)	6	1	1	8
Microsporum felineum (lanosum)	2†	0	0	2
Microsporum gypseum (fulvum)	2	0	0	2
Microsporum audouini	1	0	0	1
Trichophyton rubrum (purpureum)	0	0	1	1
Unidentified	0	0	1‡	1
No pathogenic fungi isolated	4	1	2	7
Total	24	4	11	39

* Includes 1 case of agminate folliculitis of the forearm.
† In addition, 8 cases of noninflammatory human type ringworm of the scalp yielded M. felineum on culture.
‡ Apparently a dermatophyte with unusual pigment-producing properties; the strain was lost before identification could be made.

7 cases of tinea capitis and tinea barbae due to T. mentagrophytes, the organism isolated was the deep rose, exceedingly granular variety.

REPORT AND SUMMARY OF CASES

Of the 17 patients with infections caused by T. faviforme, 15 resided on farms and the remaining 2 had visited at a farm for two weeks prior to the onset of the disease. Thirteen were children, and 3 others were in their teens. A definite history of contact with infected cattle was elicited in but a few of these patients; frequently the children and their escorts simply were not informed as to the possible contacts. The average duration of the infection before treatment was three and one-half weeks, and the average patient was well about four weeks after treatment was begun. There was a suggestion gained from the figures on duration before and after treatment that those

10. Georg: Personal communication to the author.

patients with recent infections responded a little more slowly than those whose disease was of long standing when treatment began.

Four rather typical cases are presented in more detail.

CASE 1.—R. P., a farm boy aged 9, was first seen on April 10, 1947, presenting a slowly spreading kerion of the occipital scalp of four weeks' duration. Direct examination revealed a mat of interlacing nonseptate filaments about some of the hairs and chains of large rectangular spores about others. Cultures yielded T. faviforme. Treatment consisted of manual epilation of the kerion and application of 3 per cent ammoniated mercury ointment. By April 28 the lesions were no longer pustular, the inflammation was subsiding and microscopic examination failed to reveal the fungus. Alopecia with induration persisted for several more weeks. On July 9 a pustular folliculitis appeared about the new hairs in one patch, but repeated attempts to find fungi failed and response to ammoniated mercury ointment was apparently good.

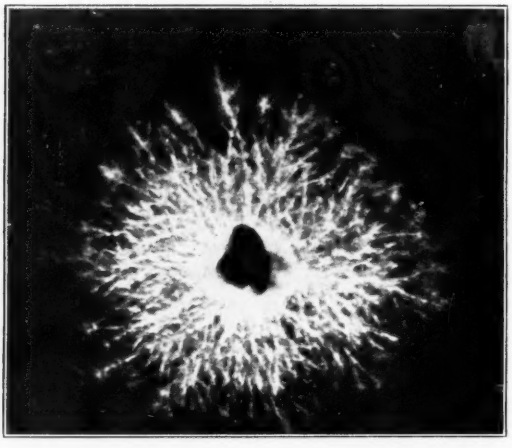

Fig. 1.—Gross appearance (× 3) of a T. faviforme culture grown on 2 per cent dextrose agar at 37 C. for about three weeks, showing the characteristic lacy subsurface growth.

CASE 2.—P. H., a farmer aged about 35, was first seen on April 25, 1946, complaining of a kerion-like sycosis of the neck and upper lip of seven weeks' duration. A large-spored ectothrix was seen on direct examination, and cultures were identified as T. faviforme. Manual epilation and application of 3 per cent ammoniated mercury ointment rendered all areas inactive by May 11, and healing was considered complete on May 18.

CASE 3.—M. C., a 9 year old girl, was first seen on July 20, 1946, presenting a widespread circinate eruption on the face, neck, back, chest and arms of two weeks' duration. Close contact with calves had occurred during the two weeks prior to the onset of the rash. The eruption consisted of annular and confluent gyrate lesions with pustular borders and partial clearing in the centers. Filaments and chains of large rectangular arthrospores were seen on direct microscopic examination of the skin scrapings. T. faviforme was isolated by culture. Treatment with

2.5 per cent salicylic acid and 5 per cent ammoniated mercury in hydrophilic ointment (U.S.P. XIII) resulted in complete recovery by August 13.

CASE 4.—S. S., a farm girl aged 5, was first seen on June 13, 1947, with a superficial spreading pustular erythematous patch, 5 cm. in diameter, about the left angle of the mouth, present three weeks. There were two smaller lesions of shorter duration on the left thigh. The child had played with infected calves. Direct microscopic examination of the scales revealed septate branching filaments and chains of arthrospores; cultures yielded T. faviforme. The treatment suggested was 2 per cent tincture of iodine diluted to one-half strength with alcohol. Healing was reported to be complete in one week.

CLINICAL CONSIDERATIONS

T. faviforme may produce inflammatory tinea capitis, particularly kerion, a kerion-like tinea barbae, and superficial inflammatory circinate

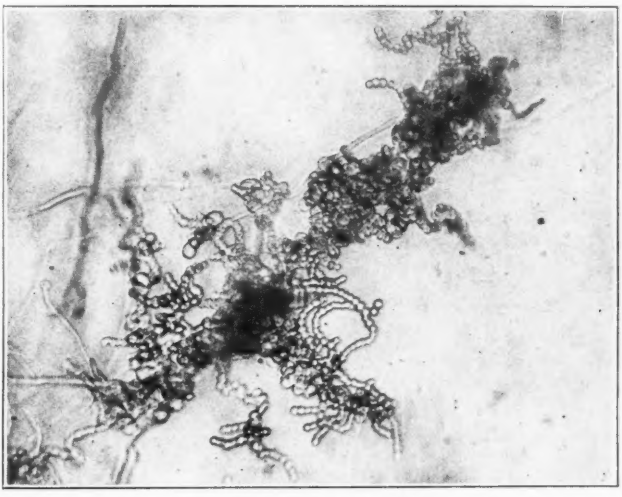

Fig. 2.—Hyphae and chains and clusters of chlamydospores on 2 per cent dextrose agar at 37 C.

tinea on the smooth skin, usually with a pustular element, as well as agminate folliculitis. Infected hairs do not fluoresce under filtered ultraviolet rays, but large spores outside the shaft of the hair can usually be noted microscopically. In pus the organism is seen as chains of large spores with a tendency to square or rectangular shape and in the skin as septate or nonseptate filaments and as clusters and chains of arthrospores. Trichophytids may occur, and the result of the trichophytin test is probably always positive in cases of well developed disease.

MYCOLOGIC STUDIES

In view of the excellent descriptions and careful research devoted to the faviform trichophyta by Georg in published and forthcoming

articles, it would seem unnecessary to attempt, in this paper, a detailed description of the fungus. A few remarks regarding technics and main cultural features may be in order.

At the present time all cases of ringworm believed to be of animal origin seen in this clinic are cultured in the following manner. Infected material, without any special treatment, is plated out on two sets of culture mediums. Each set consists of three plates, one containing 1:10,000 methyrosaniline chloride agar (included as a routine isolation medium), one 2 per cent dextrose agar and one cornmeal agar. One of these sets is kept at room temperature, and the other is incubated at 37 C. in a moist atmosphere. The plates are

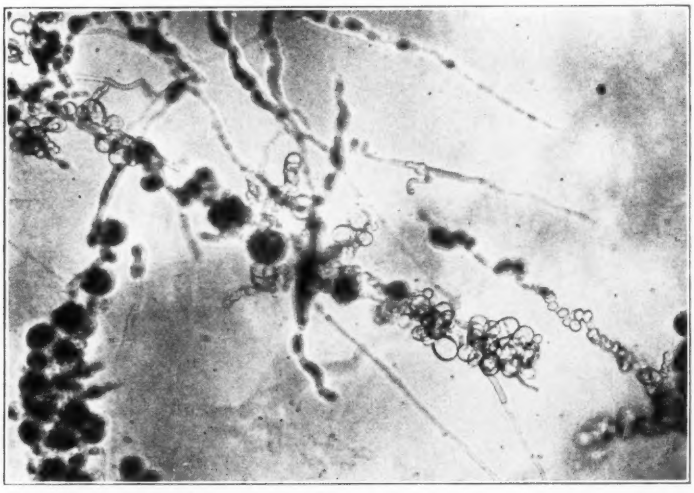

Fig. 3.—Clusters of enormous chlamydospores on 2 per cent dextrose agar at 37 C.

watched closely for the typical colony of T. faviforme, so that subcultures can be made when necessary for isolation. The colony is characteristic, especially on the incubated dextrose plate, and can be recognized macroscopically (fig. 1). It is felt that the snowflake design of the odd lacy growth, almost entirely subsurface, is unique and constitutes presumptive identification, which must be certified by subsequent microscopic and perhaps special cultural studies. Growth on cornmeal agar is scant, and none occurs on the methylrosaniline chloride medium.

Microscopically the colonies grown on dextrose agar in the incubator are characterized by the immense numbers of chlamydospores, intercalary, terminal and in long branching chains (fig. 2). Some

of the chlamydospores are extremely large (fig. 3). With the low power objective, the lacy fringes of the colony somewhat resemble fir trees in their tapering branched masses of filaments and spores. Aerial growth is almost absent, and microconidia are rarely seen. In the cultures grown at room temperature the chlamydospores are still conspicuous but far less numerous, and abortive chandeliers and wavy hyphae can be seen (fig. 4). Aerial growth is increased, though not luxuriant, and microconidia are rare to moderately numerous. Macroconidia are not encountered without special nutrient mediums.[1]

TREATMENT

Experience in the treatment in these cases proves that inflammatory ringworm caused by T. faviforme, like that due to other organ-

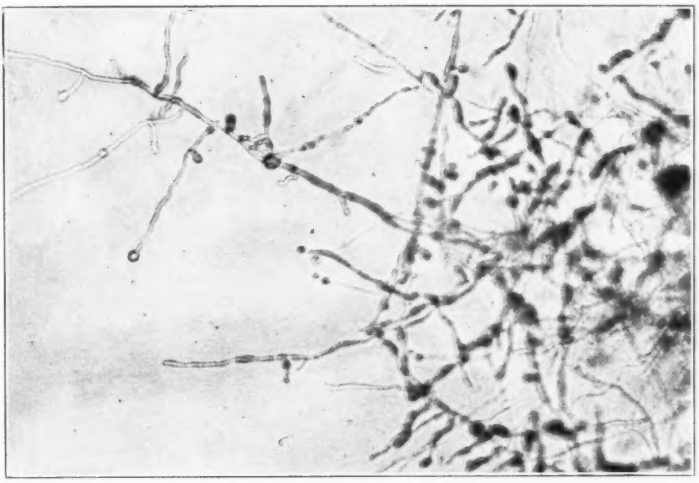

Fig. 4.—Appearance microscopically on 2 per cent dextrose agar at room temperature.

isms, is a self-limiting disease. Cure is effected more promptly by manually epilating the involved areas and a narrow zone around them. In most of these cases the task was effectively accomplished by someone in the patient's family. Special fungicides seem unnecessary, since wet dressings and simple antiseptic preparations have been sufficient. Cure probably depends to some extent on the development of an immune response in the patient. Roentgen therapy is not necessary or desirable in inflammatory ringworm, and its use may bring medicolegal complications, should permanent scarring and alopecia be produced by the infection.

SUMMARY

Of 39 cases of inflammatory ringworm of the glabrous skin, beard and scalp studied by cultural methods, 17 proved to be caused by Trichophyton faviforme, 8 by Trichophyton mentagrophytes (gypseum group), 2 by Microsporum felineum (lanosum), 2 by Microsporum gypseum (fulvum), 1 by Microsporum audouini and 1 by Trichophyton rubrum (purpureum). In 1 case the organism was unidentified, and in 7 cases cultures were unsuccessful, T. faviforme being suspected in 3 of them from the microscopic appearance of the hairs. This organism, known since 1893, has rarely been isolated in the United States—indeed, but once until 1942—but seems to be a more common cause of inflammatory ringworm than hitherto was thought. In the cases here reported manual epilation, wet dressings and mild fungicides constituted adequate treatment. Cultural and mycologic features are described.

CONCLUSIONS

Trichophyton faviforme is a more important cause of inflammatory ringworm of animal origin than previously was suspected and seems to be the most common cause in Iowa. Special cultural methods are necessary for its isolation. Trichophyton mentagrophytes (gypseum group), notably the rose-colored granular form, ranks second as a cause of inflammatory ringworm in Iowa. The animal microspora are relatively unimportant.

REITER'S SYNDROME WITH KERATOTIC DERMATITIS

Report of a Case

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PITTSBURGH

IN THE practice of the average physician, Reiter's disease, or more properly Reiter's syndrome, and the numerous polysyllabic pseudonyms under which it has from time to time been classified, e. g., nongonococcic keratoderma blennorrhagicum, keratosis blennorrhagica and idiopathic blennorrheal arthritis,[1] are rarely encountered. Although a pleomorphic syndrome, it has become sufficiently well established since it was first described in 1916[2] to be considered a clinical entity. To dermatologists, urologists, ophthalmologists and those responsible for patients with arthritis, it is a puzzling and challenging problem. The present case is reported both because of the association of dermatitis with the symptom complex and because of the unusual severity of the clinical picture.

REPORT OF CASE

Physical Examination.—K. M., a 20 year old enlisted white man, married and childless, noted a painful throbbing of his right foot on Sept. 3, 1945. The next day it was swollen and he reported to sick bay, where he gave a history of intermittent, slight stiffness, soreness and swelling of the ankles, knees and feet, without incapacitation, over a period of years. His condition was diagnosed as rheumatic fever, and he was transferred to a naval hospital on September 6. The patient denied having had venereal disease or previous acute rheumatic manifestations. His temperature was 100 F., his pulse rate 112 and his respiratory rate 18 per minute, and his blood pressure 100 systolic and 60 diastolic. He was well developed, poorly nourished and pale. The pharynx was slightly injected. A moderate funnel deformity depressed the lower part of the sternum. The genitalia were those of a normal, circumcised man except for excoriated, dry lesions on the scrotum and penis. These were seborrheic and itched considerably. The right foot was moderately swollen, slightly reddened and mildly tender, principally about the medial malleolus

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1. Sargent, J. C.: Reiter's Syndrome, J. Urol. **54**:556 (Dec.) 1945.

2. Reiter, H.: Ueber eine bisher unerkannte Spirochätinfektion (Spirochaetosis arthritica), Deutsche med. Wchnschr. **42**:1529 (Dec. 7); 1535 (Dec. 14) 1916.

and the first metatarsophalangeal joint. Limitation of motion was present without changes in temperature in the areas affected. There was also symmetric, circular swelling of the second and third metacarpophalangeal joints of the right hand, which were a little reddened and tender but not warm.

Laboratory Examination.—There was a relative polymorphonuclear leukocytosis and an increased erythrocyte sedimentation rate. The urine contained 50 mg. of albumin per hundred cubic centimeters, 10 to 15 white blood cells per high power field and a few epithelial cells.

Course.—The patient showed slow, progressive improvement during the first two weeks in the hospital, except for one episode of sore throat. A dermatologic consultant elicited a long history of scaly, itching scalp and diagnosed the genital lesions as seborrheic dermatitis. No signs of cardiac involvement appeared, and the patient was transferred to the United States Naval Hospital at Dublin, Ga., on Sept. 21, 1945.

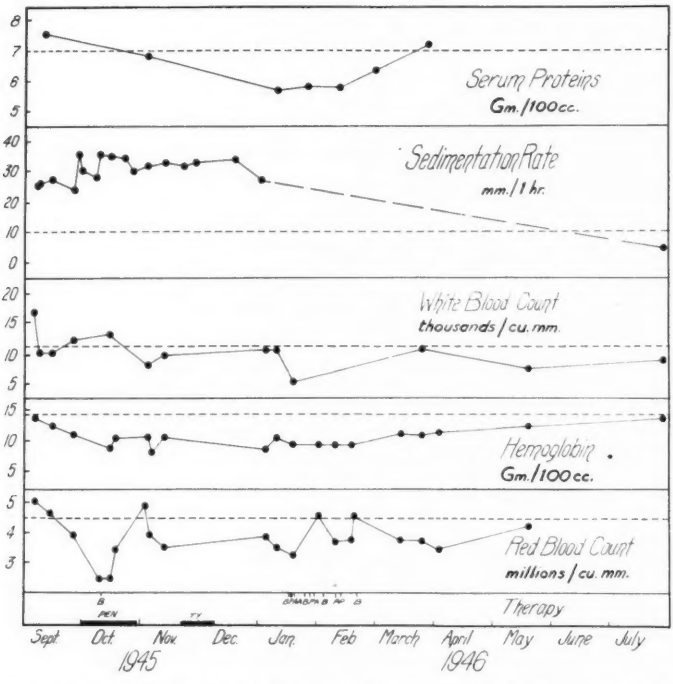

Fig. 1.—Laboratory and treatment data in the reported case. Broken lines indicate the approximate limit of normalcy for each test. *A* indicates intravenous injection of "amigen"; *B*, transfusion of whole blood (usually 1,000 cc.); *P*, transfusion of pooled plasma (usually 500 cc.); *PEN*, administration of penicillin (200,000 Oxford units daily); *TY*, administration of typhoid vaccine.

The following changes were then noted: His temperature was 100.8 F., his pulse rate 92 and his respiratory rate 20 per minute, and his blood pressure was 100 systolic and 55 diastolic. He was emaciated and pale and appeared acutely ill;

there was generalized muscular wasting. The skin of the feet, scalp and penis showed multiple scaling lesions with bright, erythematous borders. The lymph nodes in both cervical and both inguinal regions were enlarged but not tender. There was a transient, very soft, systolic murmur in the left second interspace. No urethral discharge was noted, but there was inflammatory edema of the prepuce. There was slight ulnad deviation of the right hand, and pain was felt on passive motion of the small joints of the right hand, knee and ankle. The knee joints showed signs of fluid, and the left one was tender. The right foot and ankle were swollen, with multiple petechial hemorrhages on the lateral aspect and slight pitting edema. Fusiform enlargement, pain and limitation of motion were noted in the second and third metacarpophalangeal joints of the right hand. The nails showed pitting and distal, subungual discoloration.

On September 24 stomatitis developed, resembling Vincent's infection. This cleared on daily treatment with 100,000 units of penicillin, although organisms were

Fig. 2.—Photographs of patient taken shortly after recovery started. *A*, hands, showing involvement of joints, with swelling of tissues and deformities of finger nails. The large lesion at the base of the right middle finger was previously covered by a large cutaneous horn. Several smaller horns are still present. *B*, right forearm, showing multiple small cutaneous horns at sites of venipunctures.

not found on smear. A week later daily administration of 200,000 units of penicillin was prescribed because of a slight regression in the swelling of the joints during the first course.

On October 2 the diagnosis was changed to arthritis deformans, since the course was not that of rheumatic fever. The patient's weight had fallen 37 pounds (16.8 Kg.) in one month (he now weighed 130 pounds [59 Kg.]), and a rapidly progressive anemia had appeared (fig. 1). Subjectively he improved somewhat in the next few weeks, but deformities of joints and muscular contractures began to appear. A dermatologic consultant made a diagnosis of "fungous infection of the skin and toes of both feet, seborrheic dermatitis and possibly psoriasis and eczematoid dermatitis" and prescribed a number of medicaments for local application. On October 17 cutaneous horns were noted on the body and in the axillas.

The treatment with penicillin was continued through October 29, but a sharp daily rise in temperature, to 100 or 102 F., persisted. Between November 15 and December 7 he was given injections of typhoid vaccine, after which some subjective improvement was noted. However, the lesions of the skin continued to spread.

On Jan. 2, 1946 I first saw the patient. A history of an associated, relatively benign conjunctivitis which had recurred two or three times since the onset of the illness and of an existing, mild urethritis was elicited. The patient by this time had a severely deforming arthritis of the knees, ankles, toes, fingers and wrists, with fusiform swelling, slight local heat and little redness but much tenderness. Lesions in all stages of development were seen (fig. 2). The earliest were small (1 to 2 mm), orange-yellow vesicles; at a later stage they appeared as large, orange-brown bullae, which subsequently either broke, leaving dry, red, nontender bases and flaky, white, firm edges without surrounding erythema, or progressed to form cutaneous horns, some as large as 3 cm. in diameter. The desquamations had become confluent in a butterfly distribution over the nose; over the genitalia, the surrounding areas of the thighs and the inguinal troughs, and over the distal portions of the fingers and toes. These areas were an angry red and dry, with little or no exudation. The finger nails and toe nails were wrinkled, pigmented and loosened. A diagnosis of Reiter's syndrome was made and active supportive therapy recommended.

In mid-January the daily administration of multivitamin capsules and 125,000 units of vitamin A was begun. A week later a regimen of frequent injections of "amigen" (a hydrolysate of casein prepared by digestion with sheep and hog pancreas) and transfusions of plasma was instituted (fig. 1). It was noted that small cutaneous horns had developed at the scars of the venipunctures (fig. 2 *B*).

On Jan. 22, 1946 examination revealed extreme emaciation and cachexia. The patient was unable to move his right hand and fingers, and only with difficulty could he move his arm. He complained of almost constant pain in his joints, despite large doses of sodium salicylate. The dermatitis now involved the greater part of both feet and ankles and the knee joints, as well as the scalp, face, chest, back, arms, thighs and legs. Some secondary infection was present on the feet. By mid-February the joints of the shoulders, the temporomandibular joints and the spine were involved. The skin was worse, if possible, and the patient was failing rapidly. He had a slight hemorrhage per rectum and was placed on the list of those "seriously ill." A week later he passed more bright red blood per rectum, even though he had received subcutaneous injections of a vitamin K preparation twice daily, on each of the preceding five days. Throughout this period of severe illness the conjunctivitis and the urethritis recurred frequently, usually for short periods of from one to five days (the two seldom occurred simultaneously).

Suddenly, in early March, dramatic improvement began. By April his cutaneous lesions were clearing, his appetite was normal and his weight was increasing. In May mobilization was started; in June laboratory findings were normal, and convalescent leave was permitted. In September 1946, when he was discharged from the service, his condition was described in the following summary: "'At present the patient is asymptomatic and afebrile and is getting along well, but he has residual stiffness and deformity of his fingers, wrists and toes, for which he is receiving physical therapy. Roentgenograms showed changes due to rheumatoid arthritis in the region of the proximal interphalangeal joints of both hands and narrowing of the joints of the feet. Results of all other physical and laboratory examinations were normal."

Laboratory Data.—Figure 1 summarizes the laboratory data and their relation to therapy.

The results of the following laboratory examinations, carried out during the early months of the illness, were normal.

- Kahn test
- Smears and cultures
  - Malaria (3)
  - Fungi
- Basal metabolism
- Gastric analysis for hydrochloric acid
- Agglutination tests
  - Typhoid
  - Paratyphoid
  - Typhus (Weil-Felix)
  - Brucellosis
- Examination of stools
  - Blood
  - Ova
  - Parasites
- Blood tests
  - Culture
  - Chemistry
    - Uric acid
    - Sugar
    - Nonprotein nitrogen (3)
    - Calcium

Repeated urinalyses indicated moderate numbers of epithelial and white blood cells, which gradually decreased as recovery progressed. On one occasion, 50 mg. of albumin per hundred cubic centimeters of urine was noted; on another, an olive green reaction to the test for reducing sugar. The total number of white blood cells remained above 10,000 for the first two months of the disease, fell to more normal levels and then rose again in early 1946, as the patient's clinical condition deteriorated, returning gradually to normal as recovery started (fig. 1). The differential blood count was unremarkable. Relative predominance of polymorphonuclear leukocytes reflected rises in the total number of leukocytes, the percentage regressing as the white cell count fell to normal levels. As indicated in figure 1, the rise in the number of red blood cells and in the amount of hemoglobin paralleled clinical progress, except as they were affected by blood transfusions. Electrocardiograms, taken on three occasions, were normal.

Roentgenographic Examinations.—On Oct. 4, 1945 there was swelling of the soft tissue of the right ankle. On November 5 there were moderate demineralization of all bones in the right hand and fusiform swelling of the soft tissue about all the proximal interphalangeal joints. The joint cavities were normal. There was striking formation of new periosteal bone about the distal end of the shaft of the second and third metacarpal bones. On Feb. 14, 1946 a sharp increase was observed in the extent of demineralization of the bones of the knees and ankles. The joint cavities were slightly narrowed.

On May 21 extensive changes of rheumatoid arthritis were observed, with considerable swelling of the joint capsules in the region of the proximal interphalangeal joints of both hands and with atrophy and erosion of the bone and narrowing of the joints also involving the feet. The swelling of the joint capsule was reduced, and the lesion seemed to be in an arrested stage. There was no definite evidence of ankylosis.

Roentgenograms of the chest were normal on three occasions.

Summary of Therapy.—Certain therapeutic time relations with laboratory data are indicated in figure 1. Salicylates were given in varying doses throughout the course, with interruptions. The response to analgesics was inconsistent. During the patient's periods of severest illness they seemed of little value, and codeine was repeatedly necessary. Throughout most of the course administration of 10 to 15 grains (0.65 to 0.975 Gm.) of sodium salicylate every three hours gave satisfactory relief from arthralgia. Sulfadiazine was given on at least two occasions (once with adjuvant lozenges of penicillin), without apparent effects. Penicillin did not affect the temperature or the course of the disease (fig. 1). Local treatment of the skin

included applications of ointments containing sulfur, salicylic acid, benzoic acid and sulfathiazole, in various combinations. After the first four months only boric acid ointment U. S. P., boric acid soaks and hydrous wool fat U. S. P. were used. A course of typhoid vaccine (385,000,000 organisms, administered in ten doses over a period of seventeen days) was given, without objective response. In January a series of transfusions of plasma and whole blood and injections of "amigen" was begun. Physical therapy, including local application of heat and passive stretching of the muscles, was started in February, and bivalved casts for the arms and legs were used at night. In the late spring he was placed on the regular rehabilitative regimen of the hospital, with supplementary active physical therapy.

COMMENT

In virtually all respects this case is characteristic of the syndrome described in the literature as Reiter's disease. The primary diagnostic criteria are coexisting arthritis, conjunctivitis and urethritis, associated at times with eruptions of the skin, iritis, keratitis, cystitis or disease of the upper urinary tract. Hyperkeratotic dermatitis has been reported by numerous observers [3] as occurring in these cases, although its incidence is not high. This case is one of the few in which the patient's life was seriously threatened.[3a,d] The occurrence of hyperkeratotic lesions at the sites of venipunctures has apparently not been previously reported in connection with this disease.[3'] Recently, many writers [4] have stressed the frequent occurrence of previous or intercurrent enteritis or dysentery. While my patient did not have typical dysentery at any

3. (*a*) Epstein, E.: Reiter's Disease: Comparison with Keratosis Blennorrhagica and with Psoriasis Arthropathica, Arch. Dermat. & Syph. **56**:191 (Aug.) 1947. (*b*) Hollander, J. L.; Fogarty, C. W., Jr.; Abrams, N. R., and Kydd, D. M.: Arthritis Resembling Reiter's Syndrome: Observations on Twenty-Five Cases, J. A. M. A. **129**:593 (Oct. 27) 1945. (*c*) Kuske, H.: Ueber die Hauterscheinungen bei Morbus Reiter: Ein Beitrag zur Differentialdiagnose der sog. gonorrhoischen Keratosen, Arch. f. Dermat. u. Syph. **179**:58, 1939. (*d*) Lever, W. F., and Crawford, G. M.: Keratosis Blennorrhagica Without Gonorrhea (Reiter's Disease?), Arch. Dermat. & Syph. **49**:389 (June) 1944. (*e*) Lucas R. L., and Weiss, H.: Gonorrheal Syndrome Without Gonorrhea: Reiter's Disease, Arch. Ophth. **34**:97 (Aug.) 1945. (*f*) Pinck, B. D.: Reiter's Syndrome, Am. J. M. Sc. **214**:76 (July) 1947.

3'. Since submission of this paper one other case of such lesions has been reported (Morrison, R. J. G., and Thompson, M.: Reiter's Syndrome, Lancet **1**: 636 [April 20] 1948). In this instance, the keratoses appeared at the site of injections of penicillin.

4. (*a*) Forbes, D.: Case of Reiter's Disease, Brit. M. J. **2**:859 (Dec. 7) 1946. (*b*) Herson, R. N.: Reiter's Disease, Correspondence, ibid. **2**:275 (Aug. 24) 1946. (*c*) Jackson, W. P. U.: Syndrome Known as Reiter's Disease (Triad of Polyarthritis, Urethritis and Conjunctivitis), ibid. **2**:197 (Aug. 10) 1946. (*d*) Koster, M. S., and Jansen, M. T.: Reiter's Disease, Nederl. tijdschr. v. Geneesk. **90**:483 (May 18) 1946. (*e*) Marsh, F.: Reiter's Disease, Correspondence, Brit. M. J. **2**:275 (Aug. 24) 1946. (*f*) Young, R. H., and McEwen, E. G.: Bacillary Dysentery as Cause of Arthritis with Nonspecific Urithritis and Conjunctivitis, J. A. M. A. **134**:1456 (Aug. 23) 1947.

time, acute onsets of rectal bleeding have been observed by others.[3d] The striking predilection of Reiter's syndrome for young men in military service in time of war has been noted by most observers and may or may not be partially due to the higher standards of diagnosis and of physical fitness attendant on the military induction of persons in this age group. Fifty-eight, or 76 per cent, of the cases analyzed here were those of military men or men who had their first symptoms while in service. Despite the predominance of the disease in men, Lever and Crawford [3d] reported a case of Reiter's syndrome in a woman (included in this series), and Koster and Jansen [4d] noted that other cases in women had been recorded. In only one series was the disease diagnosed in children.[4d] Cases have occurred in Europe,[5] the South

Analysis of 76 Cases of Reiter's Syndrome

	Number of Cases		Percentage	
Cases originating in military service *	58		76	
Cases with dermatitis	12		16	
Initial symptoms				
Urethritis	45	76	59.2	100
Conjunctivitis	6		7.9	
Arthritis	13		17.1	
Not determined †	12		15.8	
Cases with dysentery				
Antecedent	12	15	19.7	
During disease	1			
Time not determined	2			
Total	76			

* This number includes 3 recently discharged veterans and does not include 2 merchant seamen.

† This number includes some cases in which two initial symptoms were noted simultaneously.

Pacific,[6] North Africa,[4f] North America,[7] the Middle East [4a,b] and the Bahamas,[4c] the last being the only recorded case of the disease in a Negro.

In this paper, 76 of about 110 reported cases, including the one reported in this paper, have been analyzed, and certain of the data are presented in the accompanying table. The commonest initial symptom was urethritis, followed, in order of decreasing frequency,

5. (*a*) Reiter.[2] (*b*) Koster and Jansen.[4d] (*c*) Young and McEwen.[4f] (*d*) Wrigley, F.: Reiter's Disease, Brit. M. J. **2**:199 (Aug. 10) 1946.

6. Rosenblum, H. H.: So-Called Reiter's Disease: Triad of Acute Arthritis, Conjunctivitis, and Urethritis, U. S. Nav. M. Bull. **44**:375 (Feb.) 1945.

7. (*a*) Hollander, Fogarty, Abrams and Kydd.[3b] (*b*) Lever and Crawford.[3d] (*c*) Pinck.[3f] (*d*) Bauer, W., and Engleman, E. P.: Syndrome of Unknown Etiology Characterized by Urethritis, Conjunctivitis, and Arthritis (So-Called Reiter's Disease), Tr. A. Am. Physicians **57**:307, 1942.

by arthritis and conjunctivitis. A history of diarrhea or enteritis as a previous or intercurrent complaint was mentioned in 15 cases, or 20 per cent. An initial diagnosis of gonorrhea was observed in a large proportion of the cases; exclusion of this diagnosis was through apparently adequate bacteriologic or microscopic examination or by adequate, but unsuccessful, chemotherapy in virtually every case. The clinical course was almost always relatively benign. Severe,[3a] and even fatal,[3d] forms have occurred, however. The course of the disease is often protracted, and recurrences after prolonged remission are not infrequent.[8] (It has not been possible to learn of my patient's progress since his discharge from the service.) Attention has been drawn to a number of cases in which one of the diagnostic triad of symptoms was lacking, and it is probable that some of these represent Reiter's syndrome.[9] These cases have not been included in the analysis.

Figure 1 indicates some of the laboratory findings in the case reported. In virtually all respects they follow the pattern of the disease described in the literature. The erythrocyte sedimentation rate is increased for long periods. Leukocytosis of varying degree is the rule, although in my patient this was noticeable only at the onset of the illness. Progressive anemia and hypoproteinemia are the usual concomitants in the severer cases[1]; both were at times severe in the present case. Roentgenograms, when made, indicated disturbances in the joints of the type usually associated with rheumatoid arthritis.[10] The roentgenologist stated unequivocally that the damage to the joints in this case was far more rapidly progressive than any he had ever seen in rheumatoid arthritis.

Diagnosis at present is made through exclusion, i.e., through failure to find an infecting organism in the presence of coexisting conjunctivitis, urethritis and arthritis. In cases with associated dermatitis the differentiation from psoriatic arthritis rests on the distribution of the lesions of the skin which are not located primarily about the afflicted joints in Reiter's syndrome, and on the presence of inflammation in the urinary tract. Elimination of the gonococcus as a possible

8. (*a*) Sargent.[1] (*b*) Forbes.[4a] (*c*) Rosenblum.[6] (*d*) Bauer and Engleman.[7d] (*e*) Colby, F. H.: Renal Complications of Reiter's Disease, J. Urol. **52**:415 (Nov.) 1944. (*f*) Dunham, J.; Rock, J., and Belt, E.: Isolation of Filterable Agent Pathogenic for Mice from Case of Reiter's Disease, ibid. **58**:212 (Sept.) 1947. (*g*) Miller, C. D., and McIntyre, D. W.: Syndrome Termed Reiter's Disease (Urethritis, Conjunctivitis and Arthritis), Ann. Int. Med. **23**:673 (Oct.) 1945. (*h*) Olenick, E. J., and Sargent, J. W.: Urologic and Ophthalmologic Observations in Two Cases of Reiter's Syndrome, U. S. Nav. M. Bull. **47**:657 (July-Aug.) 1947. (*i*) Vallee, B. L.: Reiter's Disease: Review of Literature, with Presentation of Case, Arch. Int. Med. **77**:295 (March) 1946.

9. Epstein.[3a] Hollander, Fogarty, Abrams and Kydd.[3b] Jackson.[4c] Young and McEwen.[4f]

10. Bauer and Engleman.[7d] Lever and Crawford.[3d] Rosenblum.[6] Vallee.[8i]

cause is made after bacteriologic search and/or after an adequate trial of specific therapy.

Despite much effort, both speculative and investigative, expended on determining the etiology of the syndrome, little of a definitive nature can yet be stated. Although it has many of the characteristics of an infectious systemic disease, and although evidence points to a possible pleuropneumonia-like organism in its pathogenesis, adequate and complete confirmation are lacking. The similarity between certain cases of Reiter's syndrome with severe lesions of the skin and gonococcic keratotic dermatitis has led some observers to state the belief that it is a gonorrheal infection in which Neisseria gonorrhoeae, notably an evasive organism, cannot be detected. More recently, improved methods of obtaining cultures and the use of specific chemotherapeutic agents have seemed to eliminate this possibility, as in the case reported here. An outgrowth of this theory, and a natural inference from the physical resemblance of some cases of gonorrheal dermatitis, was the impression that Reiter's syndrome represented a sensitization to gonorrheal infection. Available serologic technics have not furnished any confirmatory evidence for this theory.[11] In fact, a history of antecedent gonorrheal infection, at any time, is the exception rather than the rule in these patients.[6] In no case in the group reported here was there a history of proved antecedent specific urethritis; in a few there were histories of treated gonorrhea which had not been confirmed by laboratory examination. The urethritis in Reiter's syndrome is, however, similar enough to gonorrhea to have caused at least one physician to treat himself for it, as described (in his case 3) by Colby.[8e] Other suggested causative agents include the dysentery organisms,[4e,f] spirochetes,[2] a staphylococcus,[3b] a filtrable virus,[8f] streptococci [8i] and allergic reactions to dysentery bacilli.[4a] Adequate confirmatory data are lacking for any of these.

In 1939, Findlay [12] isolated an organism of the pleuropneumonia-like group from rats involved in an epidemic of polyarthritis; other observers [13] confirmed his discovery, and similar findings in mice were reported at about the same time.[14] Subsequent investigations by Dienes

11. Hollander, Fogarty, Abrams and Kydd.[3b] Lever and Crawford.[3d] Young and McEwen.[4f] Rosenblum.[6]

12. Findlay, F. M.: Pleuropneumonia-Like Organisms and Arthritis, Ann. Rheumat. Dis. **5**:153 (Sept.) 1946.

13. (*a*) Beeuwkes, H., and Collier, W. A.: Studies on Arthrotropic Pleuropneumonia-Like Organisms, J. Infect. Dis. **70**:1 (Jan.-Feb.) 1942. (*b*) Klieneberger, E.: Pleuropneumonia-Like Organisms: Further Comparative Studies and Descriptive Account of Recently Discovered Types, J. Hyg. **40**:204 (March) 1940.

14. Beeuwkes and Collier.[13a] Klieneberger.[13b] Sabin, A. B.: Experimental Proliferative Arthritis in Mice Produced by Filtrable Pleuropneumonia-Like Microorganisms, Science **89**:228 (March 10) 1939.

and Smith [15] and by Findlay [12] revealed that these organisms were present in the genital secretions of human patients, and that they were most frequently found in victims of "nonspecific" inflammation. Changes in the joints of goats and cattle and conjunctivitis in mice have been reported during infections with these organisms.[16] Dienes and Smith,[15] in their studies of pleuropneumonia-like organisms, succeeded in isolating them from the urethral discharges of patients with arthritis and urethritis. I was unable to arrange for an adequate bacteriologic search for these organisms in the present case. Recently Wallerstein and others [17] demonstrated agglutination of a strain of pleuropneumonia-like organisms with serums of patients having symptom complexes related to and including Reiter's syndrome. Most recently Dunham and others,[8f] in 1947, reported the successful transmission of conjunctivitis to mice from a patient with Reiter's syndrome. The causative agent passed a Seitz filter and was therefore presumed to be viral, since pleuropneumonia-like organisms, which are also filtrable, could not be found.

The problem of transmission in human beings has received little attention. The infectious agent, if such exists, either is not easily passed between persons, or is not highly pathogenic. Our patient was never isolated, nor have other patients been considered infectious. Nevertheless, with 1 exception,[4d] incidents of transmission to members of patients' families, medical attendants or others in the immediate environment have not been reported. Histories of previous sexual contact with affected persons or of sexual excess have been noted repeatedly,[18] but evidence that such contacts were etiologically pertinent has not yet been presented; the findings of Dienes and Smith [15] noted in the foregoing paragraph are, however, suggestive. Any such antecedent exposure was denied by our patient. If the pleuropneumonia-like organisms ultimately are proved to be causative, investigation of possible animal vectors will be necessary, since the organisms are pathogenic or saprophytic in so many common domestic species.

Biopsy.—Microscopic studies of the skin have shown nonspecific changes compatible with the hyperkeratosis and chronic inflammation observed in the gross specimen.[3c,d] One excised lymph node revealed

15. Dienes, L., and Smith, W. E.: Relationship of Pleuropneumonia-Like (L) Organisms to Infections of Human Genital Tract, Proc. Soc. Exper. Biol. & Med. **50**:99 (May) 1942.

16. Findlay.[12] Klieneberger.[13b]

17. Wallerstein, R.; Vallee, B. L., and Turner, L.: Possible Relationship of Pleuropneumonia-Like Organisms to Reiter's Disease, J. Infect. Dis. **79**:134 (Sept.-Oct.) 1946.

18. (*a*) Sargent.[1] (*b*) Young and McEwen.[4f] (*c*) Colby.[8e] (*d*) Twiss, J. R., and Douglas, A. H. R.: Reiter's Disease: Report of Two Cases, Ann. Int. Med. **24**:1043 (June) 1946.

chronic inflammatory hypertrophy.[18d] Synovial membranes have been described as grossly hyperemic with papillary hypertrophy and with some exudate. Microscopic changes were similar to those in mild cases of synovitis.[19] The synovial fluids have been observed to be of an acute, hemorrhagic, inflammatory type.[20] Only one observer [8f] has been able to obtain pathogenic material from tissues or from fluids of the joints, despite repeated attempts by many investigators.

Therapy.—Treatment must be confined to supportive and symptomatic measures. Although the cutaneous, urethral and conjunctival lesions not infrequently contain frank pus, the presence of the usual secondary pathogens in significant numbers is so unusual as to suggest local antibiotic activity. Bacterial and fungus cultures of the lesions of the case reported here were repeatedly sterile. Usually soap and water and bland ointments, such as hydrous wool fat U. S. P., boric acid ointment or white petrolatum, are quite satisfactory, keep the patient comfortable and do not cause detectable exacerbation of local inflammation.

The urethritis is usually uncomfortable but relatively mild. Analgesia for urinary discomfort may at times be needed. Prostatitis or even rather severe disturbances of the urinary tract have been reported,[21] but specific therapeutic measures are not available, although some observers have noted a good response in these complaints to intravenous arsenical therapy in small doses.[22]

My case was typical of most in that the ocular involvement was not of major importance. Boric acid eyewashes, with or without ointment for crusting of the lids, are quite satisfactory in such cases in relieving the conjunctival irritation, which is usually virtually asymptomatic. Complications, such as iritis and keratitis, have been reported,[23] although only rarely followed by permanent residua. It is of interest to note that artificial fever therapy has been employed in many victims of Reiter's syndrome, occasionally with admirable results.[22b] Although generally of only temporary, if any, assistance, as in the author's case, and frequently useless,[1] it has been noted to cause prompt healing of ocular lesions.[8g] No explanation for this

19. Hollander, Fogarty, Abrams and Kydd.[3b] Bauer and Engleman.[7d]

20. Hollander, Fogarty, Abrams and Kydd.[3b] Lever and Crawford.[3d] Pinck.[3f]

21. Sargent.[1] Rosenblum.[6] Colby.[8e] Olenick and Sargent.[8h] Goldstein, A. E., and Rubin, S. W.: Reiter's Disease Followed by True Infective Abacterial Pyuria, Brit. J. Urol. **19**:32 (March) 1947.

22. (*a*) Moore, T.: True Infective Abacterial Pyuria, Brit. J. Urol. **17**:131 (Dec.) 1945. (*b*) Strachstein, A.: Reiter's Disease—Report of Case Successfully Treated, New York State J. Med. **45**:2190 (Oct. 15) 1945.

23. Sargent.[1] Hollander, Fogarty, Abrams and Kydd.[3b] Lucas and Weiss.[3e] Pinck.[3f] Rosenblum.[6] Bauer and Engleman.[7d] Vallee.[8i] Baxter, C. R.: Reiter's Disease, Brit. M. J. **2**:858 (Dec. 7) 1946.

apparently rather specific effect is available, although it is known that artificial fever is of value in many other types of optic inflammation.

The arthritis, if severe, requires active therapy if maximal joint salvage is to be obtained. In cases of recovery residual permanent joint damage, as suffered by the patient whose case is reported here, is the only objective finding that has been reported with significant frequency [24] with the exception of renal lesions, which may or may not be primarily related to this syndrome.[8e] The statement of certain authors [3a,b] that residual joint damage does not occur in Reiter's syndrome is in direct conflict with the reported experience of others [24] and with my experience in this case. Such permanent residua are certainly the exception rather than the rule. Patients should receive passive physical therapy and adequate analgesia for relief of muscular spasm, and casts should be applied to extremities which are sufficiently involved to threaten deformity. In the convalescent phase active exercise and heat should be added to the regimen. Loss of weight, cachexia, and secondary anemia of considerable degree frequently develop in severe cases, though seldom to the degree observed in the present case, in which these manifestations threatened to prove fatal. Transfusions, high vitamin, high protein and high caloric diets, and much careful nursing care and encouragement of the patient are indicated to preserve a maximal state of nutrition, "resistance" and morale. Prior to the institution of intensive nutritional and physical therapy, combined with transfusions of whole blood and parenteral administration of other fluids, the ward physician in the present case had been resigned to the patient's inevitable death from an incurable condition. The above mentioned therapy was accompanied with a prompt, if not dramatic, change in the entire clinical course. It is distinctly possible that the usual course of this illness might be shortened and that some of its disabling residua might be avoided if energetic supportive regimens were more commonly instituted early in the disease.

SUMMARY

A case of severe Reiter's syndrome with keratoderma is reported and an analysis of recently reported cases presented. Recent etiologic studies are discussed, and important therapeutic indications are considered.

ADDENDUM

Since the submission of this paper for publication, numerous reports of additional cases have appeared. Certain of them which include important statistics or contributions to knowledge of the disease are briefly noted.

24. Sargent.[1] Vallee.[81]

Undoubtedly the most remarkable work was that of Paronen,[25] who presented reports on 344 cases in Finland. Thus the number of reported cases is probably more than doubled by this one study, although only 233 of the cases qualify for comparison with the series presented, the remaining 111 lacking one or more of the basic triad of symptoms. Of particular significance in this "epidemic" of the disease were: (1) low incidence of cutaneous lesions; (2) typically high proportion of cases in military personnel; (3) significant rate of recurrence, despite the short period of study; (4) failure to discover an effective regimen of specific therapy, and (5) occurrence of 10 per cent of cases in female patients and of 1 case in a child. Perhaps of greatest interest was the implication of a specific organism (Shigella of Flexner) as a cause of antecedent dysentery in 96.4 per cent of the patients, despite failure to isolate viable organisms in most cases; this substantiated Wood's demonstration of sensitivity to the Flexner organism a year earlier.[26]

Florman and Goldstein reported an additional instance of the syndrome in a child 4 years of age.[27] Dienes and his associates recently summarized their data on the pleuropneumonia-like organisms, including the isolation of the organisms from joint fluid in 2 cases of Reiter's syndrome.[28] Swanson and Delaney abstracted the statistical data of the United States Navy on the disease during the war years.[29] The total number of cases for the years 1944 to 1947 reached 51, including 1 of apparent permanent disability. The first reports indicated that patients treated with streptomycin showed some improvement,[30] but, as Warthin indicated,[30b] the improvement was not sufficiently clearcut to warrant definite conclusions regarding the efficacy of streptomycin. Zewi's Finnish cases are primarily of interest in that they include several women and children and no military personnel.[31]

Lieut. Comdr. Robert Quinn (MC), U. S. N. R. prepared the photographs, and Dr. Bernard D. Pinck contributed supplementary statistical data from his series of cases.[3f]

125 DeSota Street.

25. Paronen, I.: Reiter's Disease, Acta med. Scandinav., 1948, supp. 212.

26. Wood, P.: Reiter's Disease, Brit. M. J. **2**:309 (Aug. 31) 1946.

27. Florman, A. L., and Goldstein, H. M.: Arthritis, Conjunctivitis and Urethritis (So-Called Reiter's Syndrome) in a Four-Year-Old Boy, J. Pediat. **33**:172 (Aug.) 1948.

28. Dienes, L.; Ropes, M. W.; Smith, W. E.; Madoff, S., and Bauer, W.: Role of Pleuropneumonia-like Organisms in Genitourinary and Joint Diseases, New England J. Med. **238**:509 (April 8); 563 (April 15) 1948.

29. Swanson, C. A., and Delaney, A. J.: Discussion of Reiter's Syndrome with Report of a Case, U. S. Nav. M. Bull. **48**:503 (July-Aug.) 1948.

30. (*a*) Dienes and others.[4] (*b*) Warthin, T. A.: Reiter's Syndrome: Report on Four Cases Treated with Streptomycin, Am. J. Med. **4**:827 (June) 1948.

31. Zewi, M.: Morbus Reiteri, Acta ophth. **25**:47, 1947.

UNUSUAL REACTIONS TO INTRAVENOUS INJECTIONS OF TYPHOID VACCINE

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MANY untoward reactions to the induction of fever by intravenous injections of typhoid vaccine [1] have been recorded since Miller and Lusk [2] first introduced this method of inducing fever for therapeutic purposes in 1916. Prior to the advent of penicillin therapy of syphilis, almost 3,000 patients were treated for syphilis at Bellevue Hospital with fever induced by intravenous injection of typhoid vaccine and massive arsenotherapy. Two unusual reactions were noted in the large group of patients so treated. They were not previously reported because at about the time they occurred we abandoned this type of treatment entirely. More recently a third unusual reaction to typhoid vaccine was observed in the dermatologic service at Bellevue Hospital in a patient who did not have syphilis and who received no chemotherapy. In the first 2 cases the reactions were associated with severe illness and pronounced pulmonary symptoms; the third reaction caused hemoglobinuria. The case histories follow.

REPORT OF CASES

CASE 1.—S. W., a 22 year old Negro woman, was admitted to Bellevue Hospital Jan. 16, 1945, because of primary and secondary syphilis. Results of physical examination were entirely normal except for primary and secondary syphilitic lesions. She had no history of previous serious illnesses or allergic manifestations.

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1. Hench, P. S.: Usual and Unusual Reactions to Protein (Fever) Therapy, Arch. Int. Med. **49**:1 (Jan.) 1932. Lewis, P. M.: Dangers from Non-Specific Protein Therapy, South. M. J. **34**: (June) 1941. Wallace, J., and Bushby, S. R.: Hazards of Hyperthermia Treatment, Lancet **2**:458 (Oct. 7) 1944. Cordes, T. C.: Typhoid Vaccine Therapy: Unusual Reaction; Report of One Case of Hepatorenal Syndrome, Quart. Bull., Northwestern Univ. M. School **18**:184, 1944.

2. Miller, J. L., and Lusk, F. B.: The Treatment of Arthritis by the Intravenous Injection of Foreign Protein, J. A. M. A. **66**:1756 (June 3) 1916.

A schedule of antisyphilitic treatment was started which called for intramuscular injections of 0.2 Gm. of bismuth salicylate, intravenous injections of typhoid vaccine every other day for four injections and daily injections of 0.05 Gm. of oxophenarsine hydrochloride for ten days. Her first injection of 0.1 cc. of triple typhoid vaccine contained Bacillus typhosus, 100,000,000 organisms, Bacillus paratyphosus A, 75,000,000, and Bacillus paratyphosus B, 75,000,000. After the injection a temperature of 104 F. developed, which returned to 99 F. within twelve hours. The second intravenous injection of triple typhoid vaccine was given two days later and, in accordance with the routine practice at that time, consisted of twice the original dose. After the second injection the patient had a temperature of 105.4 F., which fell to 99 F. in twelve hours. The following day decided abdominal distention developed, unassociated with nausea, tenderness or rigidity. No further injections of oxophenarsine hydrochloride, bismuth compound or typhoid vaccine were given. After two days the abdominal distention subsided, but the patient

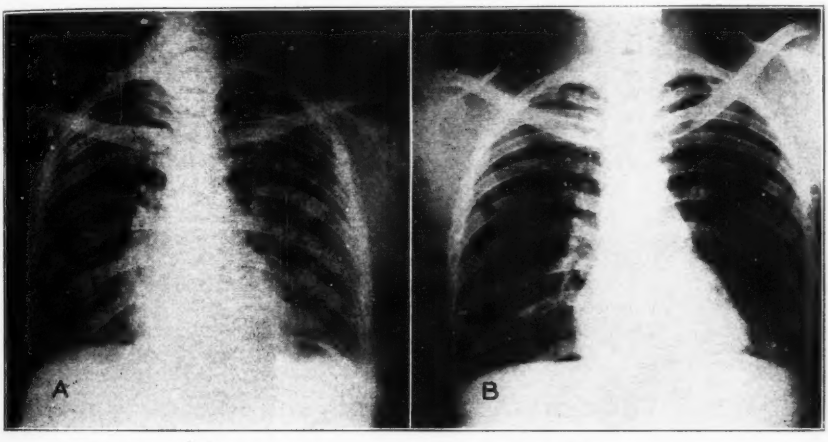

Fig. 1 (case 1).—*A*, roentgenogram taken Jan. 23, 1945. *B*, roentgenogram taken Feb. 10, 1945.

was stuporous, acutely ill and dyspneic. There were no evidences of consolidation of the lungs, but rales were heard over the lower half of both lungs. A roentgenogram of the chest taken on January 23, the fourth day after her second injection of typhoid vaccine, showed a disseminated infiltration involving the major portion of both lungs (fig. 1 *A*). The infiltrations resembled a miliary spread, but the size of the nodules and the fact that the apexes of both lungs were clear made the diagnosis of miliary tuberculosis improbable. The patient continued to be acutely ill, dyspneic and tachypneic for five days, after which she gradually improved. During the episode her respirations varied from 30 to 52 per minute and the pulse rate varied between 120 and 150 per minute. The blood pressure was low, varying from 90 systolic and 70 diastolic to 98 systolic and 72 diastolic. The temperature remained between 101 F. and 103.6 F. for ten days and then became normal and remained normal for the next two weeks while the patient remained in the hospital. The lungs became completely clear by February 10 (fig. 1 *B*).

During the reaction the patient's erythrocyte sedimentation rate increased from 35 to 120 mm. per hour. The white blood cell count varied between 13,400 and 11,500, with 68 per cent polymorphonuclear leukocytes, 18 per cent lymphocytes, 10 per cent large monocytes and 2 per cent eosinophils. The red blood cell count was 4,500,000, and the hemoglobin was 15 Gm. Examination of the spinal fluid during the episode gave entirely normal results. Electrocardiograms were normal except for evidence of tachycardia. The result of a patch test with typhoid vaccine was negative, but intradermal injection of very dilute typhoid vaccine produced decided erythema and wheal formation.

CASE 2.—M. M., a single Negro girl of 16 years of age, was admitted to Bellevue Hospital Feb. 1, 1945, because of secondary syphilis. Except for evidences of secondary syphilis in both skin and mucous membranes the results of her physical examination were normal. She gave no history of previous serious

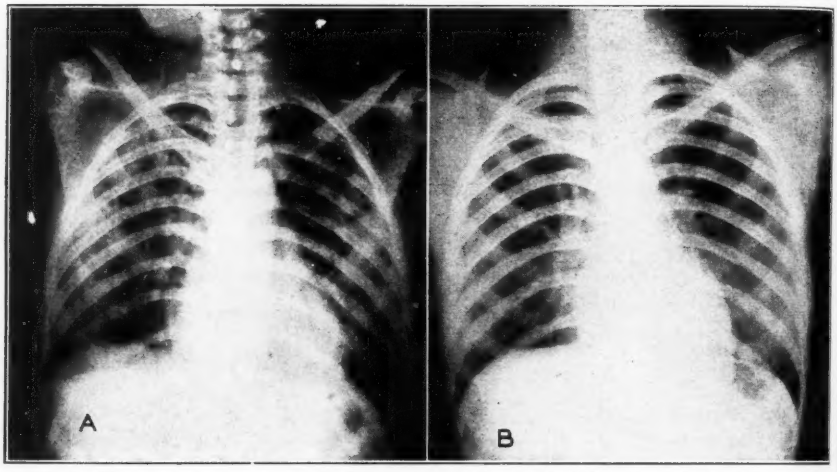

Fig. 2 (case 2).—*A*, roentgenogram showing patchy infiltration of the lungs. *B*, roentgenogram of Feb. 20, 1945, showing no abnormalities.

illnesses and no history of allergic manifestations. Antisyphilitic treatment was started on February 3 with daily injections of 0.06 Gm. of oxophenarsine hydrochloride. She received her first intravenous injection of 0.1 cc. of triple typhoid vaccine on February 5, following which she had a temperature of 105 F., which became normal within eight hours. A second intravenous injection of 0.2 cc. of triple typhoid vaccine was given on February 7, following which she had a temperature of 104 F., which became normal within ten hours. On the following day she complained of generalized muscle pains, and her temperature rose to 101 F. that evening. Treatment with oxophenarsine hydrochloride was discontinued and she was given 20,000 units of penicillin every three hours. On the next day, February 9, she appeared acutely ill and complained of pain in the back and chest. Her temperature remained at about 102 F. On February 10, she complained of a headache and continued to have a temperature between 102 and 103 F. Physical examination revealed no signs in the lungs and no abdominal distention, rigidity or tenderness. On the morning of February 11, she seemed no worse than the day

before until the afternoon, when she suddenly became dyspneic; the respirations were shallow and rapid, between 50 and 60 per minute. Her pulse rate was 140, and her chief complaint was generalized abdominal pain. The physical examination revealed no rales in the lungs and no evidence of pneumonia; the abdomen was slightly tender, but there was no distention or rigidity. On the next day, however, her abdomen was distended and rigid and she bled from the nose and vagina. She was stuporous and unable to answer questions. The scleras were icteric, and a few rales were heard in both lungs. Her temperature varied between 103 and 104 F. The pulse rate was between 120 and 140. The blood pressure was 120 systolic and 80 diastolic. Her hemoglobin was 12 Gm., the red cell count was 3,000,000 and the white cell count 5,000, with 41 per cent polymorphonuclear leukocytes, 35 per cent lymphocytes, 22 per cent large monocytes and 2 per cent eosinophils. Platelets were normal. Bleeding time was reported as 5 minutes and clotting time as 4½ minutes. Results of tests for sickling of red blood cells were negative. The urinalysis showed albumin (2 plus), urobilinogen positive in dilutions of 1 to 60 and many red blood cells. The nonprotein nitrogen of the blood was 25 mg. per hundred cubic centimeters, and the blood urea was 9 mg. per hundred cubic centimeters. The icteric index was 40. A roentgenogram of the chest showed a patchy infiltration of both lungs (fig. 2 *A*). The patient continued to have dyspnea, tachycardia, fever and mild jaundice with bleeding from the mucous membranes for the next four days and then gradually began to recover. The icteric index was never over 40, but her red cell count fell to as low as 2,200,000 and the white cell count to 3,700. She was treated with intramuscular injections of crude liver extract, 100 mg. of ascorbic acid and 5 mg. of vitamin K daily. Her temperature remained elevated for nine days and the blood cell count, bleeding time, clotting time, icteric index and urinary observations all became normal within three weeks after the onset of her reaction. The icterus was probably due to hemolysis of red blood cells. By February 20 the roentgenogram of the lungs revealed no abnormalities (fig. 2 *B*). After the reaction, results of patch tests with typhoid vaccine were negative. No intradermal test was done.

COMMENT

Both of the aforementioned reactions are believed to be due to the typhoid vaccine rather than to oxophenarsine hydrochloride. The pulmonary signs and symptoms were most unusual. Hartman and Major [3] described decided pulmonary congestion and hemorrhages in dogs in which high rectal temperatures, between 107 and 110 F., were maintained for five to seven hours, but the patients reported by us did not have unusually high or prolonged temperatures following the injections of typhoid vaccine.

Harkavy [4] described pulmonary changes with an interstitial type of patchy involvement of the lungs which he ascribed to vascular

3. Hartman, F. W., and Major R. C.: Pathological Changes Resulting from Controlled Artificial Fever, Am. J. Clin. Path. **5**:392 (Sept.) 1935.

4. Harkavy, J.: Vascular Allergy: Pathogenesis of Bronchial Asthma with Recurrent Pulmonary Infiltrations and Eosinophilic Polyserositis, Arch. Int. Med. **67**:709 (April) 1941; Vascular Allergy, J. Mt. Sinai Hosp. **8**:592 (Jan.) 1942; Vascular Allergy, J. Allergy **14**:507 (Nov.) 1943.

hyperergy following sensitization to some antigen. The shadows of the roentgenograms in the cases reported by Harkavy lacked the homogeneous character of those produced in bronchopneumonia and resembled hematogenous rather than alveolar lesions. In cases which came to autopsy, the histopathologic observations consisted of pulmonary infiltrations due to congestion and edema. The most significant pathologic lesion in the lungs was the degree of hyperergic reaction in the pulmonary vessels, which varied from simple thickening of small vessels involving the intima to acute necrotizing arteritis.

Our 2 patients apparently had reactions similar to those reported by Harkavy as vascular allergy, and we must assume that they were sensitized to the typhoid vaccine. It is unusual, however, for persons to become sensitized as rapidly as the 2 patients observed by us. In both symptoms began to develop on the day following a second intravenous injection of typhoid vaccine, which was given three days after the first injection in 1 case and two days after the first injection in the other. The fact that both of these unusual reactions occurred within a month of each other suggested that the typhoid vaccine then in use might have been at fault, but other patients who received intravenous injections of the same lot of vaccine had no untoward reactions. Apparently the reactions must be interpreted as hyperergic phenomena.

REACTION WITH HEMOGLOBINURIA

The third unusual reaction to typhoid vaccine was not associated with pulmonary signs or symptoms but with hemoglobinuria.

CASE 3.—R. L., a 37 year old male Negro, was admitted to Bellevue Hospital Jan. 5, 1947, because of atopic dermatitis. His past history revealed no serious illnesses and no allergic manifestations. The results of physical examination were normal except for the cutaneous condition. Results of urinalyses and blood cell count were normal before therapy with intravenous injections of typhoid vaccine was started.

The first intravenous injection of 0.08 cc. typhoid vaccine consisted of Bacillus typhosus, 800,000 organisms, following which a temperature of 103 F. developed. Two days later a second injection of B. typhosus, 1,500,000 organisms, was given intravenously. The temperature rose to 105.2 F., and the patient became stuporous and was in mild shock. He was given an intravenous infusion of 5 per cent dextrose in isotonic sodium chloride solution and improved, but that evening he passed about 1,000 cc. of brown urine. Results of both guaiac and benzidine tests of the urine were strongly positive; microscopic examination revealed granular casts and a few leukocytes, but only rare red blood cells. The patient continued to have fever, malaise and hemoglobinuria for the next three days. At no time was there any clinical jaundice, and the urine was free from bile. The icteric index was normal. There was no sickling of red blood cells. Results of tests for cold agglutinin were negative. The lungs were clear, and he had no pulmonary symptoms. He received intravenous infusions, and, in view of the

work of Ham and his co-workers[5] on nocturnal hemoglobinuria, sodium bicarbonate by mouth in large doses was given. The urinary discoloration subsided in a few days.

COMMENT

We have found no other report of hemoglobinuria due to typhoid vaccine in the literature. This patient did not receive chemotherapy, and the hemoglobinuria must be attributed to the vaccine. The clinical course was similar to that in the hemoglobinuria described in the "crush syndrome."

SUMMARY

Two cases of severe reactions to intravenous injections of typhoid vaccine and oxophenarsine hydrochloride are reported, both of which were associated with unusual pulmonary symptoms. One case of hemoglobinuria following intravenous injection of typhoid vaccine is reported.

5. Ham, T. H.: Studies on Destruction of Red Blood Cells: Chronic Hemolytic Anemia with Paroxysmal Nocturnal Hemoglobinuria, Arch. Int. Med. **64**:1271 (Dec.) 1939.

Clinical Notes

STAINING OF FUNGI IN SCALES AND HAIRS

Method of Staining with Polychrome Methylene Blue

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Staining methods are of much less practical importance in medical mycology than in bacteriology. Bacteria must be stained, as a rule, in order to be seen. Fungi, especially the superficial cutaneous pathogens, can be observed without staining in preparations cleared in an aqueous solution of potassium hydroxide, and the efficiency, simplicity and speed with which it may be done have made this method of examination popular in routine mycologic work. Staining of fungi in hairs and scrapings from the skin or nails requires more complex equipment and more time, and often not all fungi present in a specimen are stained equally well. The keratinized cells resist the penetration of dyes and make it difficult to stain fungi inside hairs, scales and hard fragments of nails. The stained preparations possess, however, several important advantages as compared with specimens cleared in potassium hydroxide. The stained preparations are permanent. They reveal the fine morphologic details of fungi more distinctly. They allow the use of higher magnification, including the oil immersion objective. They give better results in microphotography and microprojection. In a case of erythrasma the potassium hydroxide method fails and staining is necessary to prove the presence of the causative organism, Actinomyces minutissimus.

The method of staining with polychrome methylene blue herein described is suitable for hairs, scales and nail scrapings. The technic is not an original one. It is a combination of procedures described by Sabouraud, Herxheimer, Unna, Bruhns, Alexander and others.[1] To my knowledge this method is not mentioned in textbooks on medical mycology published in this country.[2]

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1. Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1928, vol. 11. Bruhns, C., and Alexander A.: Grundriss der mycologishen Diagnostic, ibid., 1932.

2. (*a*) Conant, N. F.; Martin, D. S.; Smith, D. T.; Baker, R. D., and Calloway, J. L.: Manual of Clinical Mycology, Philadelphia, W. B. Saunders Company, 1944. (*b*) Dodge, C. W.: Medical Mycology: Fungous Diseases of Man and Other Mammals, St. Louis, C. V. Mosby Company, 1935. (*c*) Henrici, A. T.: Molds, Yeasts and Actinomycetes, New York, John Wiley & Sons, Inc., 1930. (*d*) Jacobson, H. P.: Fungous Diseases, Springfield, Ill., Charles C Thomas, Publisher, 1932. (*e*) Lewis, G. M., and Hopper, M. E.: An Introduction to Medical Mycology, Chicago, The Year Book Publishers, Inc., 1943. (*f*) Swartz, J. H.: Elements of Medical Mycology, New York, Grune & Stratton, Inc., 1943.

TECHNIC OF STAINING

1. *Preparation of the Material.*—The scales and the nail scrapings should be broken into the smallest particles to facilitate the contact of the dye with fungi. The hairs, separated one from another and freed from the adherent scales, should be left intact in order to preserve the natural structure and disposition of fungi in and around the hair.

Fig. 1.—Microsporon audouini in a hair from the scalp. Stained with polychrome methylene blue (× 770).

2. *Pasting of the Material on a Slide.*—The separated scales and hairs cannot be manipulated conveniently through the many steps of the staining procedure. Therefore, the material should be pasted on a microscopic slide, so that it will not be washed off until the staining has been completed. The raw egg white is a good pasting medium. Carefully separated from the yolk and kept in a well closed container, it can be preserved for a long time and will suffice

for many specimens. It is sticky, dries rapidly and holds the material firmly attached to the slide. A drop of it is spread over the center of a slide by means of a small camel hair brush. The scales and the hairs are rapidly transferred onto the sticky surface of the slide while it is still wet. The scales should be disposed in a thin layer. The hairs should not overlap one another. The size

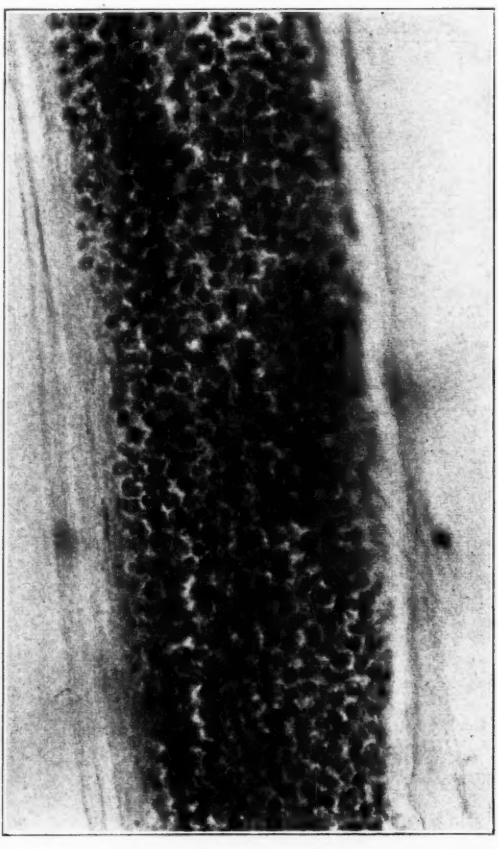

Fig. 2.—Trichophyton violaceum in a hair from the scalp. Stained with polychrome methylene blue (× 770).

of the area covered with the material should correspond to the size of the cover glass which will be applied when the staining has been completed. The preparation is then dried for a few minutes in the air or above a gas flame.

3. *Defatting and Fixation.*—The scales and the hairs usually contain fatty substances from the secretion of the sebaceous and sweat glands. This fat must

be removed to facilitate the penetration of the dye, and the protoplasm of fungi and tissue elements must be fixed before the dye is used. Both, defatting and fixation, are achieved by means of Carnoys fluid, which consists of 10 per cent of glacial acetic acid, 30 per cent of chloroform and 60 per cent of absolute alcohol. This liquid is poured onto the slide, left for five minutes and poured off and then the slide is dried in the air or above a gas flame.

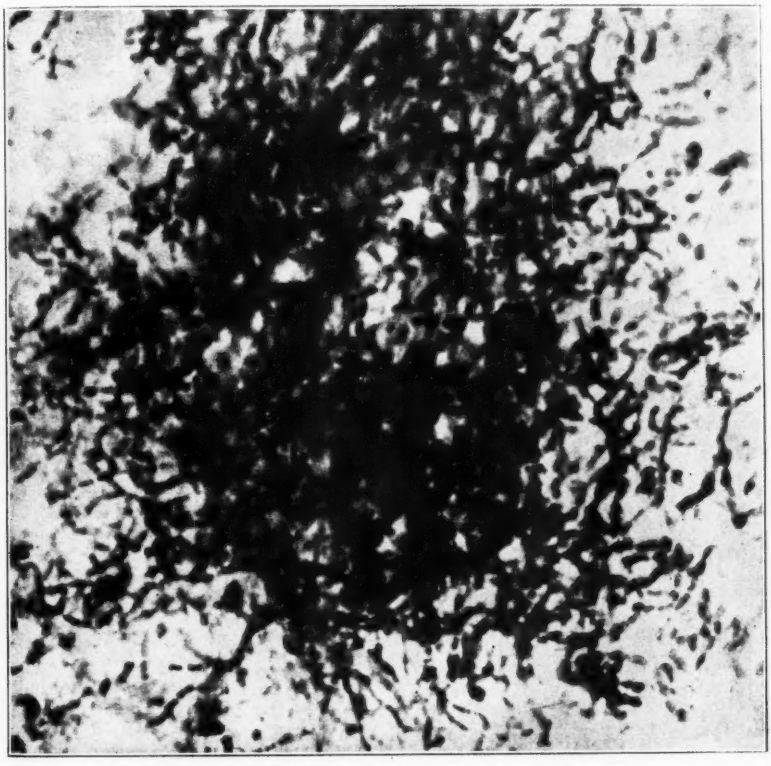

Fig. 3.—Achorion schoenleinii in a scutulum from the scalp. Stained with polychrome methylene blue (× 770).

4. *Staining.*—After many experiments with Giemsa's stain, Leffler's methylene blue and polychrome methylene blue were used; the last dye was found most satisfactory. It is poured onto the preparation, left for five minutes, poured off and is followed by washing in water.

5. *Washing in Water.*—This is done for one or two minutes. Tap water can be used, and care should be taken not to wash the material off the slide.

6. *Decolorizing.*—This is the most delicate phase of the entire operation. One per cent aqueous solution of acetic acid is used to extract the dye from the epithelial cells and hairs. Fungi, bacteria and nuclei of cells and leukocytes retain the dye and stand out distinctly on a nearly colorless background. The acid solution is left on the preparation for not more than one or two minutes. A longer exposure will decolorize everything. Then follow by:

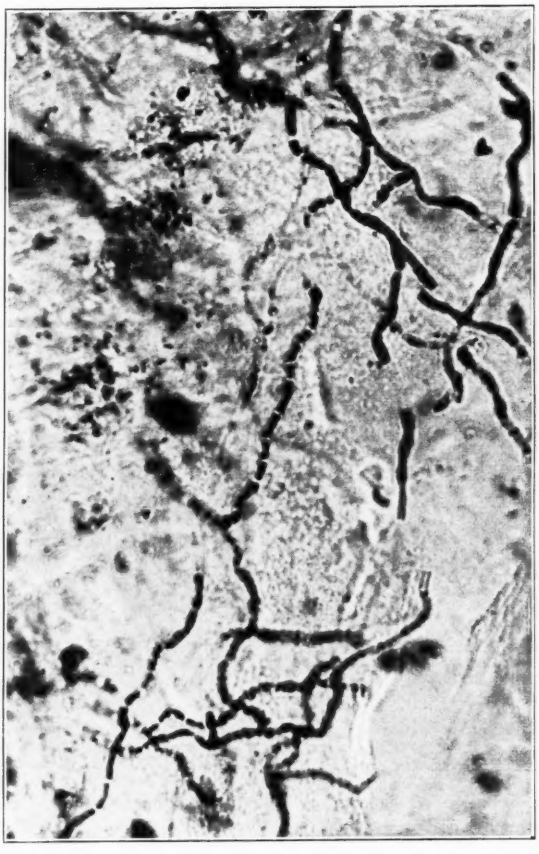

Fig. 4.—Trichophyton purpureum in scales from tinea cruris. Stained with polychrome methylene blue (× 770).

7. *Washing in Water.*—The preparation is then washed in water (one to two minutes).

8. *Absolute Alcohol.*—Absolute alcohol is then used (five minutes).

9. *Xylol.*—Xylol (dimenthylbenzene) is used for the next step (five minutes).

10. *Mounting in Canada Balsam or Clarite.*®—The specimen is then mounted in Canada balsam or clarite® (synthetic mounting medium in which aniline dyes do not fade rapidly).

The time necessary for staining of a single preparation is about forty minutes. Several preparations can be handled simultaneously, and thus time can be saved.

Fig. 5.—Malassezia furfur in scales from tinea versicolor. Stained with polychrome methylene blue (× 770).

Fungi and bacteria are stained purple or bluish purple. Nuclei of leukocytes and epithelial cells are bluish or greenish. The hair shaft is brown-green. The epithelial cells appear either colorless or faintly bluish, purplish or greenish. The variations in color are due to various intensity of staining and decolorizing. The results obtained by this method are shown in several photomicrographs.

SUMMARY

A method of staining fungi in scales and hairs by means of polychrome methylene blue is described. The procedure and the time necessary for it are as follows: (1) preparation of the material (breaking up of scales), five minutes; (2) pasting of the material on a slide by means of raw egg white and drying, three minutes; (3) fixation and defatting in Carnoy's fluid and drying, ten minutes; (4) staining with polychrome methylene blue, five minutes; (5) washing in water, two minutes; (6) decolorizing with 1 per cent aqueous solution of acetic acid, one to two minutes; (7) washing in water, two minutes; (8) washing in absolute alcohol, five minutes; (9) washing in xylol (dimethylbenzene), five minutes; and (10) mounting in Canada balsam or clarite,® two minutes.

Fig. 6.—Actinomyces minutissimus in scales from erythrasma. Stained with polychrome methylene blue (× 1550, oil immersion).

PRURITUS ANI AND/OR PRURITUS VULVAE

Its Treatment with Coparaffinate Ointment

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AND
H. N. COLE Jr., M.D.
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Pruritus ani and/or pruritus vulvae is a common disease which frequently taxes the therapeutic ingenuity of the physician. Patients are frequently annoyed to the point of exasperation by the intolerable itching, which results in loss of sleep, nervousness, irritability and loss of efficiency. The prognosis is often unfavorable, and recurrences are frequent.

The causes are numerous, and many times complex, and fall within the separate fields of internal medicine, gynecology, proctology, neurology and dermatology. However, almost invariably these patients possess symptomatic manifestations that bring them under the care of a dermatologist.

Against a background of rather unsatisfactory therapeutic results in many cases, there came to our notice in 1943 a preparation, coparaffinate ointment (ointment iso-par coparaffinate®), for which were claimed a number of properties which would, if satisfactorily demonstrated, counteract the objective and subjective symptoms in many cases of pruritus ani and, perhaps, of pruritus vulvae.

The active ingredients of the compound are complexes of certain phenolic amines and acidic oxidation products of petroleum hydrocarbons. It is claimed by the manufacturer that these particular complexes when applied to superficial lesions of the skin perform several functions simultaneously, namely, those of a superficial mild anesthetic for the terminal nerve endings, a bacteriocide for certain bacteria and a fungicide for some of the pathogenic fungi. The amines used with the acidic oxidation products of the petroleum hydrocarbons are hydroxybenzyl nonaromatic amines.

The chemical is incorporated in an ointment vehicle consisting of cetyl alcohol, white wax U. S. P., titanium dioxide, hydrous wool fat U. S.P., petrolatum and essential oils. The ointment has a rather pungent odor, which is objectionable to a small percentage of the patients.

SUMMARY OF CASES

This report is based on 168 cases in which follow-up visits were sufficient for evaluation of the effects of treatment. There were 119 cases of pruritus ani, of which 90 were of men and 29 of women. Duration of symptoms was from one month to twenty years, with an average of 3.6 years. The ages of the patients varied from 21 to 78, with an average of 45 years.

There were 36 cases of pruritus ani et vulvae and 13 cases of pruritus vulvae. In addition to perianal pruritus, there was involvement of the scrotum in 13 cases. Tinea cruris was an associated condition in 12 cases. Extension into the intergluteal area, in various degrees, was present in 26 cases. In the cases of pruritus ani studied the following associated conditions were observed: hemorrhoidal change, in 33; fissures, in 16; seborrheic dermatitis, in 14; psoriasis, in 4; fistula, in 2; diabetes, in 2; radiodermatitis, in 2; chronic colitis, in 1; pin-

worm infection, in 1, and lichen planus, in 1. An associated contact dermatitis resulting from previous medication was present or suspected in 35 cases, and nail lacquer dermatitis was the cause or an aggravating factor in 10. Vaginitis and vaginal discharge due to infection with trichomonas were seen in some of the cases of pruritus vulvae. Overindulgence in alcohol, uncleanliness, harsh toilet paper, tight-fitting underwear (jockey type shorts) and sweating in obese persons were also contributing factors.

In 96 of the chronic cases, lichenization, excoriations and thickening of the perianal or vulvar skin were present. Frequently there was secondary infectious dermatitis with edema, maceration and evidence of low grade infection.

Cultures for fungi were made in only a few instances, and the results were only occasionally positive, even in those cases in which dermatophytosis of the hands and/or feet and groins was present. In a few cases of infection with Trichophyton rubrum the disease was much more rebellious to treatment.

In the cases included in this study the condition was from one month to twenty years in duration. Often the patients had received treatments of many kinds, including roentgen irradiation and almost every conceivable type of topical application. Thus, as a result of the therapy for the dermatitis, there had been added a hypersensitivity to other agents that might be employed for future treatment.

TREATMENT

Rigid cleanliness is an important factor in the treatment of this condition. Cleansing with warm boric acid solution or an oily detergent is sometimes preferable to the use of soap and water. The parts should never be vigorously scrubbed with a washcloth or towel. If the causative factor is determined, it must be corrected. Sitz baths or compresses of potassium permanganate or boric acid solution, warm or cool, are sometimes helpful. The underwear should be light and airy, and the use of knit jockey type shorts should be avoided. Constipation should be treated by dietary measures and the use of mild cathartics. In some cases the correction of hemorrhoids, fissures and fistulas is indicated.

Coparaffinate ointment is applied lightly at bedtime after careful cleansing. If previous roentgen ray treatments did not preclude it in the series under discussion, the patients were given concomitant radiation therapy, a dose of 38 to 50 r of low voltage (100 kilovolts) unfiltered radiation being given every two or three weeks. One to eleven treatments were given, the average number being three and one-quarter treatments per patient.

In 127 cases treatment consisted in a combination of roentgen irradiation and applications of coparaffinate ointment, and in 41, in the use of coparaffinate ointment without radiation.

RESULTS OF TREATMENT

In the group of 127 cases in which the combined treatment was used, complete relief of the objective and subjective symptoms was obtained in 40, or 33.1 per cent, and decided improvement in 67, or 50.3 per cent. In those cases in which there was apparent cure, there were 8 relapses, with satisfactory results when further treatment of the same type was given. Thus cure or symptomatic relief was obtained in 107, or 85 per cent, of the 127 cases. As a rule, better results were achieved in treatment of pruritus ani than in that of pruritus vulvae.

Of 41 cases in which coparaffinate ointment alone was used, roentgen ray therapy being omitted because of previous irradiation, complete relief of objective and subjective symptoms was obtained in 9, or 22 per cent, and clinical improvement in 20, or 49 per cent. Thus the treatment was of benefit in 71 per cent of cases.

Roentgen ray therapy is of considerable value as an adjunct in the treatment of pruritus ani and/or pruritus vulvae, its effectiveness probably resulting in part from an antipruritic and stimulating effect. Small doses are just as effective as larger ones, and great care must be used to shield off surrounding parts during the treatment.

In 22 of a total of 168 cases of pruritus ani and/or pruritus vulvae in this series, there was little or no improvement, and in 10 cases the ointment was sooner or later irritating, as was evidenced by exacerbation of symptoms. In most of these instances the patients presented acute symptoms. In our opinion, coparaffinate ointment should not be employed in cases of acute pruritus, particularly that involving the vulva.

COMMENT

In women, menstruation, the menopause and the postmenopausal state appear to be etiologic or aggravating factors in cases of pruritus ani et vulvae. In men, as already mentioned, the wearing of tightly fitting jockey type shorts predisposes to overheating, perspiration and maceration of the tissues, these conditions making an ideal background for a mycotic infection.

Particularly difficult to manage are those cases in which a psychosomatic background is presented. There were 14 such cases in this series. In 16 cases examination revealed no obvious objective clinical manifestations—there was simply an intolerable pruritus. Pinworms could not be found. Treatment in these cases was often difficult.

Again, one often notes prompt symptomatic relief before the pathologic processes are cleared up.

In 5 cases the odor of the ointment was objectionable, and other topical applications were substituted.

Our experience over a period of four years with the use of coparaffinate ointment in the treatment of pruritus ani and, to a somewhat smaller extent, in that of pruritus vulvae, has convinced us that this preparation is of definite value in the treatment of these conditions.

1352 Hanna Building (15).

STREPTOMYCIN, CAUSE OF DERMATITIS VENENATA IN A NURSE

Report of a Case

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AND
HELEN PRATT DAVIS, M.D.
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Streptomycin may cause toxic erythema,[1] flushing,[2] urticaria,[2] erythema nodosum.[2c] pruritus,[3] conjunctivitis,[4] exfoliative dermatitis,[5] maculopapular [6] and

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1. Herrell, W. E., and Nichols, D. R.: The Clinical Use of Streptomycin: A Study of Forty-Five Cases, Proc. Staff Meet., Mayo Clin. **20**:449-462 (Sept. 28) 1945.

2. (*a*) Herrell and Nichols.[1] (*b*) Heilman, D. H.; Heilman, F. R.; Hinshaw, C. H.; Nichols, D. R., and Herrell, W. E.: Streptomycin: Absorption, Diffusion, Excretion, and Toxicity, Am. J. M. Sc. **210**:576-584 (Nov.) 1945. (*c*) Hettig, R. A., and Adcock, J. D.: Studies on the Toxicity of Streptomycin for Man: A Preliminary Report, Science **103**:355-357 (March 22) 1946.

(Footnotes continued on next page)

hemorrhagic [7] cutaneous eruptions. At the site of the injection swelling, erythema, heat, pain [3] and burning [2a] as well as regional adenitis [8] and thrombosis [2b] have been reported. Dermatitis venenata [3] has been noted in workers manufacturing this antibiotic. Since Paine and his group [7] found in a review of 291 papers on streptomycin that aforementioned reactions did not follow its ingestion, inhalation or local application, it is important to present this case of dermatitis venenata in a nurse who made and administered solutions of streptomycin.

REPORT OF A CASE

R. E. B., a 34 year old graduate nurse, was admitted to the department of dermatology and syphilology on May 5, 1947, complaining of a dermatitis of the fingers of three weeks' duration as well as pruritus of the face. Questioning revealed that she had noticed a mild generalized pruritus for several weeks before the onset of the localized eruption. The past history of diseases revealed occasional attacks of mild urticaria. The dermatologic examination revealed fissuring, erythema, swelling and weeping of the fifth finger of the right hand and of the third finger of the left hand. Local therapy with wet dressings was instituted with some benefit. Suddenly, four days later, there appeared pronounced swelling, scaling, crusting and erythema about both eyes. The left eye was swollen completely shut. The dermatitis of the two hands was no longer limited to the two fingers but was present on all the fingers. After being off duty for ten days, the condition about the eyes cleared except for slight scaling and pigmentation, and the hands improved. At this time a diagnosis of dermatitis venenata was made, and the patient was referred to the department of allergy, where patch tests were done with soaps and medicaments used on the floor. At the end of twenty-four and forty-eight hours, only the reaction to the patch test with streptomycin [9] was positive. At this time it was determined that for six months the nurse not only had made solutions of various lots of streptomycin but also had administered it intramuscularly and by aerosol. On return to duty she gave no streptomycin the first day and remained clear. On the second day she gave one injection of the antibiotic, and within three hours her eyelids began to itch and swell. Pruritus and dermatitis of the hands started to reappear at the same time. She again went off duty for a week with improvement in her condition. At this time, patch tests with serial dilutions of streptomycin [9] were made. In twenty-four hours, results of patch tests were positive up to the 1:100 dilution and in forty-eight hours up to the 1:1000 dilution. There was a recurrence of generalized

3. Nichols, D. R., and Herrell, W. E.: Streptomycin, J. A. M. A. **132:** 200-206 (Sept. 28) 1946.

4. Farrington, R. F.; Hull-Smith, H.; Bunn, P. A., and McDermott, W.: Streptomycin Toxicity, J. A. M. A. **134:**679-688 (June 21) 1947.

5. Davenport, L. F.: Streptomycin in Pulmonary Tuberculosis, Bull. New England M. Center **9:**83-86, 1947.

6 Heilman, Heilman, Henshaw, Nichols and Herrell.[2b] Hettig and Adcock.[2c] Nichols and Herrell.[3] Farrington, Hull-Smith, Bunn and McDermott.[4]

7. Paine, T. F.; Murray, R., and Finland, M.: Streptomycin, New England J. Med. **236:**748-760 (May 15) 1947.

8. Madigan, D. G.; Swift, P. N., and Brownlee, G.: Clinical and Pharmacological Aspects of the Toxicity of Streptomycin, Lancet **1:**9-11 (Jan. 4) 1947.

9. Merck and Company, Rahway, N. J., streptomycin lot 717.

pruritus while the patch tests were on the skin. The nurse was then placed on duty in another building where all contacts remained the same except for streptomycin. Her skin continued to clear, and there was no recurrence in one month. Later attempts to place this nurse back on duty administering streptomycin have caused new acute flareups of dermatitis venenata. Eleven other nurses who had daily contact with streptomycin were given patch tests with the same lot of the drug.[9] All had negative results.

COMMENT

Streptomycin was found to be the cause of acute dermatitis venenata of the hands and the eyes of a nurse who had administered solutions of the drug for six months before any real symptoms of cutaneous sensitivity became apparent. Individual sensitivity was demonstrated by strongly positive reactions to patch tests on the patient contrasted with negative results of patch tests in eleven nurses who also handled the antibiotic under similar conditions. Removing the nurse from the floor gave immediate relief. Allowing her to resume her previous duties caused new flareups. It is hoped that this case report will alert users of the drug to the potentialities of dermatitis venenata.

LUPUS ERYTHEMATOSUS OF THE CONJUNCTIVA AND LID MARGIN

Report of a Case

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There have been few reports by English and American writers on lupus erythematosus of the conjunctivas. In 1932, Klauder and DeLong [1] reported 3 cases of lupus erythematosus of the conjunctiva, eyelid and lid margin. They stated that the few reports of cases up to that time were made by foreign writers. In 1 of their patients there was extreme redness of the conjunctiva of the upper lids. The diagnosis of lupus erythematosus of the conjunctivas was suggested by observations of typical lesions of the disease elsewhere. They noted that on the margin of the lids there was a superficial resemblance to blepharitis and considered the following features as characteristic: ". . . adherent scales; color is red or violaceous, less red and inflammatory than blepharitis, and there is no matting of the eyelids. Later, the margins are atrophic, their surfaces being irregular; the red or violaceous color disappears, and the cilia are permanently destroyed. Since atrophy caused by lupus erythematosus is not of a contractile nature, ectropion and eversion of the lid margins are not likely to occur."

Montgomery [2] reported a case of lupus erythematosus of the conjunctiva, face and upper lip. He emphasized the fact that it is important that one recog-

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1. Klauder, J. V., and DeLong, P.: Lupus Erythematosus of the Conjunctiva, Eyelid and Lid Margin, Arch. Dermat. & Syph. **7**:856-867 (June) 1932.

2. Montgomery, D. W.: Lupus Erythematosus of the Conjunctiva, Arch. Dermat. & Syph. **37**:417-419 (March) 1938.

nize the disease, although it is rare, because of the irritable conjuntivitis which is obstinate to local treatments, a favorable response to gold sodium thiosulfate was noted in his case.

Klauder and DeLong [1] stated that to their knowledge, an isolated involvement of the conjunctivas had not been reported. The following reported case, we believe, represents an example of chronic discoid lupus erythematosus, with the initial lesions occurring on the conjunctivas and lid margins.

REPORT OF CASE

History.—Miss I. V., a white woman aged 33, was referred to us by an ophthalmologist on March 22, 1946, with complaints of a burning sensation of the left eye and a rash of the face.

The patient's past, personal and family histories were irrelevant. She had been well until September 1945. At this time she first noticed redness of the margin of the left lower eyelid. She was treated by three different ophthalmologists without relief. During this time the conjunctiva of both eyes became rather red and a burning itching sensation developed, most noticeable in the morning.

Three weeks prior to her first visit to our office, a red itching slightly scaling eruption of the left cheek was noticed. She did not recall any particularly prolonged exposure to sunlight.

The patient presented a few blotchy erythematous scaly patches of the left cheek. There were mild conjunctivitis bilaterally and diffuse redness of the lid margins. The pupils were round and equal and reacted well to light and accommodation.

Treatment and Course.—Since the facial lesions were those of chronic discoid lupus erythematosis treatment with a bismuth preparation was started. Lesions continued to develop on both sides of the face and bridge of the nose, and there were sensitive red scaly patches of the vermilion border of the lower lip. Treatment with a gold compound was then tried, with gradual improvement of the skin and ocular lesions. By August 1946 the patient was completely well; she had no further symptoms until May 1947. At this time she again noticed a slight redness of the left conjunctiva and lower lid margin. Further therapy resulted in gradual involution of the lesions, and at the time of writing the patient was practically symptom free.

SUMMARY AND CONCLUSIONS

A case of chronic discoid lupus erythematosus is presented in which ocular lesions preceded the facial eruption by many months. The patient responded well to treatment with bismuth and gold preparations.

Although the disease is undoubtedly rare, this case appears worthy of reporting in order to emphasize the consideration of lupus erythematosus in cases of refractory conjunctivitis and blepharitis.

We agree with Montgomery [2] that the disease is rather obstinate to local treatment and recognition appears important in view of the greater probability of relief afforded by systemic therapy.

OTITIS EXTERNA DUE TO OXYURIS VERMICULARIS

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Syverton and his co-workers,[1] in a study of sixteen normal ears and 72 cases of external otitis on Guam, using a wide range of culture mediums, cultured none of the so-called pathogenic fungi. The organisms found in the normal ears were those accepted as being normally present in the external ear canal. Fungi of limited pathogenicity, such as actinomyces, aspergilli, and Monilia tropicalis, were cultured in 25 per cent of those cases in which there was otitis externa. Potentially pathogenic bacteria, such as Pseudomonas aeruginosa (two thirds of the cases), Klebsiella ozaenae, Staphylococcus aureus hemolyticus, proteus and phytomonas, were isolated in all but 2 of the cases in which there was otitis externa.

Salvin and his co-workers[2] confirmed this in 100 cases studied in this country. Sharp and his co-workers[3] observed none of the so-called pathogenic fungi in 40 cases though they found the contaminated fungi in almost every case. The role of fungi in the causation of otitis externa has been greatly overstressed. The term otomycosis as used by the otologists is a misnomer and should be dropped from medical literature.

Injudicious treatment and overtreatment with topical application of seborrheic dermatitis and eczema psoriasis, impetigo and eczema of the external auditory canal is a frequent cause of otitis externa. Ear picking and scratching with such objects as sulfur-tipped match heads, finger nail polish, enamel on bobby pins and nickle on safety pins is a common habit in persons affected.

Sir Phillip Manson-Bahr[4] noted that Oxyuris vermicularis (threadworm or pinworm) is found occasionally in the nose and ears in persons in the tropics. The purpose of this paper is to present a case of otitis externa caused by this organism.

REPORT OF A CASE

Chief Complaint.—J. C. B., a man aged 28, a captain in the United States Army, was seen in February 1946, when on terminal leave, with the chief complaint of pruritus and discharge from both ears. While he was in Burma late in 1945, mild pruritis and discharge from both ears were noticed. He had had no treatment and gave no history of pruritus ani.

Past History.—He gave no history of otitis media, broken ear drum, mastoid or otitis externa prior to this.

Physical Examination.—The results of physical examination were entirely negative except for the ears. Both drums were intact, and the hearing was normal.

1. Syverton, J. T.; Hess, W. R., and Krafchuk, J.: Otitis Externa, Arch. Otolaryng. **43**:213-225 (March) 1946.

2. Salvin, S. B., and Lewis, M. L.: J. Bact. **51**:495-506 (April) 1946.

3. Sharp, W. B.; John, M. B., and Robinson, J. M.: Texas State J. Med. **42**:380-384 (Oct.) 1946.

4. Manson-Bahr, P.: Synopsis of Tropical Medicine, Baltimore, Williams & Wilkins Company, 1943.

There were scaling and erythema about the external auditory meatus extending up the canals. There was no swelling or edema of the external auditory canal. There was a slight odorless seroceruminous discharge from both ears. Microscopic examination of this diluted with water revealed numerous motile threadlike worms which were determined to be a genus of Ox. vermicularis (pinworm or threadworm). No ova were found. No ova were observed in the dirt from beneath his nails. Results of a careful search for ova about the anal orifice were negative. No adult worms were seen in the stool.

Treatment and Subsequent Course.—The ears were cleaned with alcohol and cotton. A few drops of 20 per cent benzyl benzoate in calamine lotion were instilled in both ears twice daily for two weeks. At that time the symptoms had subsided, and the man remained well for at least one year.

LIFE CYCLE OF OXYURIS VERMICULARIS

Infection takes place by one's swallowing the ova. Autoinfection is common, especially in children; the ova cling to the fingernails after scratching of the anal orifice. This makes the cure difficult. The diagnosis at times can be made by observation of the ova in the dirt beneath the nails. The ova, 50 by 15 to 25 microns, hatch and mature in the small intestine. The adult female, 9 to 12 mm. long, and the male organism, 3 to 5 mm. long, inhabit the large intestine, especially the cecum. Here at times they have been known to perforate the appendix, leading to a secondary bacterial appendicitis. The adult worms are often seen in the feces, particularly after a copious enema; the ova are rarely found. The adult female worm wanders out of the rectum, especially at night, and lays her eggs in the skin at the margin of the anus. This is the cause of the intense itching associated with this condition. The ova are usually found by scraping the skin at the margin of the anus with a dull knife. The intense pruritus, especially in children, is often the cause of neuroses, nightmares, masturbation, tics and bedwetting.

The adult female worm at times migrates from the anal area in women to the vulva, causing vaginitis, pruritus, inflammation and leukorrhea. They may migrate into the uterus, fallopian tubes and even the peritoneum, where they have caused peritonitis. In children they may cause intertriginous eczema about the genitocrural area.

In addition to autoinfection, the ova are at times carried by the nails, after scratching, to the nose and ears, where they may set up intense pruritus and irritation. Particularly in the tropics, it is wise to rule out pinworms in all cases of pruritis about the anus, vulva, nose and ears.